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Rhode Island **MEDICINE**

July 1993


Volume 76, Number 7



Medical Education in Rhode Island

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Cover: Portrait of Giovanni Battista Morgani, MD, FRS, (1692-1772). Graduate of the University of Bologna and acknowledged founder of the science of pathological anatomy.

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Medical Education: Providence and Bologna

As of early 1993, 2747 graduates of schools of medicine were licensed to practice in Rhode Island. The preponderance of these physicians (68.5%) had attended US medical schools, with Tufts (186), Brown (174), Boston University (110), State University of New York (109), Georgetown (87) and Harvard (69) contributing the most practitioners for this state. Among those educated abroad, one school dominates, the University of Bologna, providing RI with 79 physicians.

The first medical school in the Atlantic colonies was established at the University of Pennsylvania in 1765, a decade before the American Revolution. But while these colonial students were absorbing the art of medicine in Philadelphia, their counterparts in the city of Bologna could point, with justifiable pride, to their own school, which had been graduating physicians for more than 400 years.

The University of Bologna, acknowledged as the oldest university in the world providing uninterrupted higher education to the present day, began its operation in the early 12th century as a center for the study of Roman jurisprudence. The Bologna *studium* provided regular, private lessons to those men (and women) of letters interested in the law, particularly the Justinian *Corpus Juris Civilis*. This 6th century set of laws formed the fundamental text for tutorial classes, with the teachers adding their personal interpretations, the latter called *glossae*. The early faculty, sometimes referred to as the *glossatori*, consisted of such scholars as Pepo and Irnerius. Many of the students were foreigners, and upon their graduation from Bologna they became instrumental in devising the various codes of civil law adopted by most nations of western

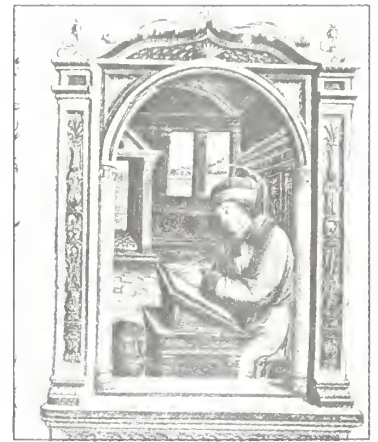
Europe, including England.

The study of canon law soon followed, together with the academic response for training scholars capable of legitimizing personal and civil agreements. These individuals, called the *notariato*, evolved into a class of public officials vested with the legal authority of witnessing the signing of documents and given the responsibility of creating registries for their safe keeping.

By the late 12th century, the number of students in Bologna had exceeded 3000 and included such scholars as Dante and Petrarch.

Chairs in human anatomy, philosophy and rhetoric were created in the 14th century, thus enabling Bologna to become the first center of higher learning to enlarge its purpose by embracing a multitude of the liberal arts, to become a *studium generale*—a true university. Among the many students from distant lands to be attracted to this academic center was the Polish astronomer-physician, Nicolaus Copernicus.

In all of these centuries of academic ferment and accomplishment, the University of Bologna still had no formal home other than the apartments of its teaching faculty. It wasn't until the 15th century that some semblance of a stable campus was established in the buildings of San Petronius. By the mid-16th century, some of the teaching facilities in Bologna, particularly the teaching of medicine, were gathered in the newly constructed *Archiginnasio*, a rectangular baroque structure surrounding an inner courtyard and incorporating the great *Teatro Anatomico*. In this hallowed prosection room (damaged during World War II but now reconstructed) Andreas Vesalius lectured on gross anatomy and Marcello Malpighi, the father of micro-anatomy, taught his students about the circulatory system and the won-



ders of microscopy.

During the early years of the 18th century, Giovanni Morgagni (see cover illustration) attended Bologna, receiving a dual doctorate in both philosophy and medicine. Morgagni (a student, incidentally, of Valsalva) remained as a teacher both in Bologna and Padua; he undertook a systematic study of abnormal anatomy in his many patients, correlating his necropsy findings with those external signs and symptoms recorded during life. These case observations culminated in the renown four-volume text *De sedibus et causis morborum per anatomen indagato*, completed in the 80th year of his long and productive life. These texts, published in 1761, represent the origins of the science of pathology.

This great university continues to flourish through the 20th century. Among its more recent graduates have been such scientists as Galvani and Marconi, as well as the 79 Rhode Island physicians who received their formal medical training in Bologna.

Brown University maintains close ties with Bologna; many Brown undergraduates, majoring in Italian studies, participate in an academic exchange program, headed by Professor Anthony Oldcorn, and devote a full year in studies on the Bologna campus. Brown has established a small liaison office in Bologna (Via del Castello 16) and would welcome visitors from Providence.

Stanley M. Aronson, MD

Brief Clinical Observations

Most journals of clinical medicine regularly publish case reports. The stimulus to submit such reports, however, is more often prompted by their

exotic uniqueness than by their educational merit. Unlikely combinations of uncommon illnesses dominate the world of published case histories. And if our clinical perceptions were to rest solely on the population described in published case reports, we surely would have a distorted perception of human disease.

The editorial board of RHODE ISLAND MEDICINE generally discourages case reports particularly if their purpose is to immortalize a clinical event of such rarity that none of the readership will likely see it in a lifetime of busy practice. If, however, a brief report can provide some lesson in diagnostic acuity, some therapeutic insight, then its publication is justified. The board recognizes, of course, the fuzzy line between cases that are interesting and those that are singular.

Beginning with this issue, Fred Schiffman, MD, shall be editing a new column for RHODE ISLAND MEDICINE, called "Brief Clinical Observations." The emphasis of these brief reports will be on the observation itself, with little discussion or extensive bibliographic review.

It is a rare practitioner who has not encountered clinical events worthy of sharing with colleagues. Our readers, accordingly, are encouraged to submit their experiences, in the form of a brief report, to Fred J. Schiffman, MD, Department of Medicine, The Miriam Hospital, Providence RI 02906, for his consideration. Eventually, RHODE ISLAND MEDICINE hopes to publish such case reports at monthly intervals.

A Misplaced Courtesy

Some 60 years ago *The New York Times* declared that its news columns were henceforth to be nonjudgmental. Accordingly, it required its reporters to refer to all public personages, revered or despised, either by their full name (eg, Adolph Hitler), by their assigned title (eg, Marshal Stalin) or by a courteously proper salutation (eg, Mr Mussolini). And in such manner did the great newspaper display its objectivity, thus restricting its judgments solely to its editorial page. This admirable policy of blanket courtesy continues today.

A small element of this practice of uniform courtesy is now evident in the way some patients, particularly males,

are described by our current house staff in their oral presentations. Decades ago a clinical summary might have begun with the words, "The patient was an elderly male who . . ." Today, we hear: "A gentleman, aged 74, came to the emergency room because of . . ." This newer verbiage—referring to all men as "gentlemen"—follows from the laudable belief that all humans seeking medical help shall be regarded with sensitivity and dignity; that their individuality be resolutely preserved; that they shall be addressed civilly (and never by first name only); and that they all shall be considered ladies and gentlemen as a consistent description.

How did our professional predecessors handle the salutation of their patients? Richard C. Cabot, MD, one of the senior physicians at Massachusetts General Hospital at the turn of

this century, published two volumes on clinical diagnosis, constituting the cornerstone of that great educational tool, the clinical pathological conference. These two volumes set out summaries of 685 cases, a case presentation custom that persists to this day in the *New England Journal of Medicine*. When the first sentences of these cases are analyzed, we see a dense concentration of possibly important clinical information packed into a few words. More often than not, this first sentence gives us the following data: Gender, occupation, age, ethnic origin, place of birth and sometimes religion (eg, "An unmarried Irish housemaid of 23 entered the hospital ...") Admittedly, some quaint turn of the century prejudices entered into Cabot's presenting sentences. Unmarried women were always referred to as "girls" until some ill-defined age of

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about 40. Males were called "boys" (or lads) until they became gainfully occupied at which time they assumed the name of their livelihood (eg, "This longshoreman aged 18 . . ." or, "This native-born white laborer, aged 17 . . .") Marital status was invariably stated with women patients, but only occasionally with men patients (akin, perhaps, to the inconstant wearing of wedding rings by married men). If foreign-born, the country of origin was invariably mentioned. It was often mentioned, too, with native born, if they were of Mediterranean ancestry. Color seemed to be a constant item to be noted (eg, "A colored widow . . ."), but "white" was employed as an adjective only if some doubt existed (eg, "A 71-year-old white Portuguese fisherman . . .") Religion was identified only if the patient was Jewish (eg, "A highly neurotic Jewish boy of 17 . . .") Diagnostic adjectives were rarely employed in this introductory sentence (eg, alcoholic, distraught, elderly, emaciated). In only one case history (No. 277) did Dr. Cabot use the word "gentleman." This particular patient was "a gentleman of 49" who was not gainfully employed but had independent means permitting him to travel the world extensively. His final diagnosis, incidentally, was spinal syphilis. One may conclude that Cabot regarded the word "gentleman" as a euphemism for an unemployed but financially self-sufficient male. Cabot sometimes used the word "lady," most often in describing an elderly woman.

The clinical pathological conferences of the 1930s continued this practice of providing gender, age, ethnicity and occupation in the first sentence. Religion, however, was no longer mentioned. By the mid-1960s the presenting sentence in the *New England Journal of Medicine* columns had been further reduced to a bare, neutral statement of gender and age; occupation was now rarely noted and ethnicity was disclosed within the details of the physical findings.

Which brings us back to the custom of describing all male patients as "gentlemen." Are they all truly gentlemen (ie, "civilized, educated, sensitive, well-mannered")? Would it not be more accurate to say "male?" If, however, the unqualified word "male" is objectionable (since it might define

living creatures other than human beings), might the word "man" be used instead? Certainly calling someone a "man" is not demeaning. It conveys a certain biological reality; it denotes gender without imparting any quality not verifiable by customary observation. It neither embellishes nor presumes. It adds no gratuitous gentility. And most assuredly it doesn't provide clinically irrelevant (if not wholly inaccurate) information. To paraphrase Burns, "A man's a man for all that."

When the patient is female, the currently used salutations seem more direct and honest. Most physicians use the word "girl" up to the threshold of sexual maturity and then switch to the word "woman." The word "lady" is almost never employed.

Calling a male patient a man provides the educated listener with some critical information without presump-

tions or ill-conceived courtesies; furthermore, it refrains from saying anything about social standing, level of education, economic status or mannerisms unless personally attested to by the examiner and relevant to the medical issue under discussion. And, very important, the word "man" preserves the dignity of the patient. All of us who have ever been hospitalized will recall the distasteful experience of an employee, often the age of our grandchildren, calling us by our first name. *The New York Times* has a good point: Be civil, be objective and leave unverified judgments to others. The paper always referred to Stalin as Mr Stalin—but never as "a 69-year-old gentleman residing in the Kremlin." Clinical conferences are exercises in mutual education and not opportunities for politically correct politeness. Stanley M. Aronson, MD

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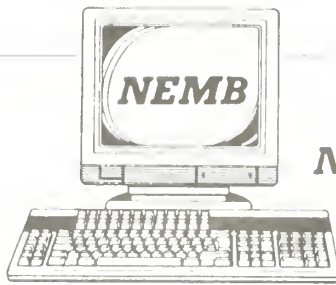
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The Brown University School of Medicine

Class of 1993

Stephen R. Smith, MD

On May 31, 1993, 76 men and women received the Doctor of Medicine degree from Brown University representing the 18th class of physicians graduated from that institution in this century. If this class follows the pattern of preceding classes, 11% eventually will enter the practice of medicine in Rhode Island. Of the 1255 physician graduates of previous classes, 205 currently are practicing in Rhode Island, including interns and residents.

Since many will be your future professional colleagues, we shall introduce the graduates of the MD Class of 1993 to the physician community in Rhode Island.

A Portrait of the Class of '93

Forty-eight graduates are men (63.2%) and 28 are women (36.8%), about the same proportion as the previous year. Historically, the balance between the sexes has been closer. Excluding this year's graduates, the rest of the medical student body is 47% female.

The racial and ethnic composition of the class (Table 1) shows more diversity than the previous class and is more in line with historical trends. Almost 12% of the graduates are members of minority groups underrepresented in medicine (8 African-American and 1 Mexican-American) as defined by the Association of American Medical Colleges. Of note is the rising proportion of the class who are Asian-Americans (18.4%). This should continue to increase since about half of the students in the first 4 undergraduate years of the 8-year Program in Liberal

Stephen R. Smith, MD, is Associate Dean for Medical Education and Professor of Family Medicine with the Brown University School of Medicine, Providence, Rhode Island.

Medical Education (PLME) are Asian-American.

About one-quarter of the class are Rhode Island residents (18 graduates representing 24% of the class). The Rhode Island students in this year's graduating class came from 13 different communities in the state, with 5 from Providence, 2 from North Providence, and 1 each from Bristol, Coventry, Cranston, Cumberland, Little Compton, Pawtucket, Saunderstown, Slatersville, Warren, West Kingston, and Woonsocket. The high schools from which the students graduated equally reflect this diversity, with 3 students each having attended Classical High School and Moses Brown School, 2 from La Salle Academy, and the rest having come from 10 other high schools.

The MD Class of 1993 included the first large PLME cohort, 21 students in all, representing 28% of the gradu-

... approximately 11% will eventually enter the practice of medicine in the state of Rhode Island.

ates. The first 60 PLME students matriculated in 1985. Five PLME students who undertook accelerated programs were graduated with previous classes, 6 transferred to other medical schools, 11 changed career goals while undergraduates, and 4 were separated from the program for academic or personal difficulties.

This class saw the last of the cohort of students admitted from the 7-year Medical Education Program (MEP). Three of the graduates were MEP students. The 8-year Program in Liberal Medical Education has replaced the MEP as the major route of admission.

The medical school entered into special agreements with four postbaccalaureate premedical programs (Bennington College, Brown University, Bryn Mawr College, and Columbia University) shortly after the PLME was inaugurated. Students from these programs decided upon a career in medicine only after completing college. Typically, they have been engaged in other careers for several years following college. The goals in establishing this new route of admission were to maintain a rich diversity in the student body by admitting students who were older and who had different academic and life experiences as well as rounding out the total class size to compensate for the expected attrition from the PLME.

Postbaccalaureate students represented 16% of the graduates. Of the 12 postbaccalaureate students, 1 came from Bennington College, 3 from Bryn Mawr College, and 4 each from Brown and Columbia.

Traditionally admitted students from 4-year undergraduate premedi-

Table 1—Demographic Characteristics of the M.D. Graduates of the Brown University School of Medicine Class of 1993

	No.	Percent
Sex		
Male	48	63.2
Female	28	36.8
Race		
White	49	64.4
Asian	14	18.4
African-American	8	10.5
Mexican-American	1	1.3
Hispanic	1	1.3
Portuguese-Am.	3	3.9
State of Residence		
Rhode Island	18	23.7
New York	16	21.1
Massachusetts	10	13.2
California	6	7.9
Pennsylvania	6	7.9
New Jersey	3	3.9
Maryland	2	2.6
Mississippi	2	2.6
Texas	2	2.6
Other States	11	14.5

ABBREVIATIONS USED:
MEP: Medical Education Program
PLME: Program in Liberal Medical Education

Table 2.—Specialty Choices of the M.D. Graduates of the Brown University School of Medicine Classes of 1989-93

Specialty Choice	Graduating Class									
	1989		1990		1991		1992		1993	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Primary Care, total	31	(38.8)	34	(44.2)	29	(38.7)	43	(56.6)	33	(45.8)
Internal Medicine, total	20	(25.0)	15	(19.5)	15	(20.0)	22	(28.9)	20	(27.8)
Categorical Medicine	14	(17.5)	13	(16.9)	13	(17.3)	16	(21.1)	16	(22.2)
Primary Care Medicine	6	(7.5)	2	(2.6)	2	(2.7)	6	(7.9)	4	(5.6)
Pediatrics	7	(8.8)	10	(13.0)	10	(13.3)	11	(14.5)	4	(5.6)
Family Medicine	4	(5.0)	8	(10.4)	4	(5.3)	10	(13.2)	9	(12.5)
Medicine/Pediatrics	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Surgery	6	(7.5)	10	(13.0)	9	(12.0)	2	(2.6)	2	(2.8)
Surgical Subspecialties, total	15	(18.8)	4	(5.2)	6	(8.0)	9	(11.8)	10	(13.9)
Ophthalmology	6	(7.5)	3	(3.9)	3	(4.0)	6	(7.9)	2	(2.8)
Orthopedics	4	(5.0)	0	(0.0)	2	(2.7)	1	(1.3)	3	(4.2)
Neurosurgery	2	(2.5)	0	(0.0)	0	(0.0)	1	(1.3)	1	(1.4)
Urology	1	(1.3)	1	(1.3)	1	(1.3)	0	(0.0)	2	(2.8)
Plastic Surgery	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)
Otorhinolaryngology	1	(1.3)	1	(1.3)	1	(1.3)	1	(1.3)	1	(1.4)
Emergency Medicine	2	(2.5)	1	(1.3)	3	(4.0)	3	(3.9)	2	(2.8)
Obstetrics & Gynecology	7	(8.8)	4	(5.2)	8	(10.7)	6	(7.9)	6	(8.3)
Psychiatry	3	(3.8)	1	(1.3)	2	(2.7)	4	(5.3)	3	(4.2)
Neurology	3	(3.8)	1	(1.3)	2	(2.7)	3	(3.9)	3	(4.2)
Transitional	2	(2.5)	7	(9.1)	3	(4.0)	1	(1.3)	8	(11.1)
Institutional Specialties, total	9	(11.3)	13	(16.9)	10	(13.3)	5	(6.6)	5	(6.9)
Anesthesiology	4	(5.0)	3	(3.9)	1	(1.3)	1	(1.3)	2	(2.8)
Pathology	1	(1.3)	0	(0.0)	1	(1.3)	2	(2.6)	1	(1.4)
Rehabilitation Medicine	0	(0.0)	1	(1.3)	1	(1.3)	1	(1.3)	1	(1.4)
Radiology	4	(5.0)	9	(11.7)	7	(9.3)	1	(1.3)	1	(1.4)
Totals*	80	(100.3)	77	(100.1)	75	(99.9)	76	(99.8)	72	(100.0)

*Excludes those not entering residency training in the same year of graduation. Totals do not add to 100.0 due to rounding

cal programs accounted for 13 members of the class (17%).

Another 16 students (21.1%) were members of the Brown/Dartmouth Medical Program in which the students spend their first 2 years of medical school at Dartmouth before completing their last 2 years at Brown.

The remainder of the class was composed of two MD/PhD students and two students who were part of the Early Identification Program at Tougaloo College, a historically black college in Jackson, Mississippi. These latter students were offered provisional admission to the medical school during their sophomore year at Tougaloo College.

Brown University was the most common undergraduate college among the graduates accounting for 36 graduates (47%). Providence College and the University of California at Berkeley ranked second with three members of the Class of 1993 having those schools as their alma mater. Altogether, the graduates of the Class of 1993

came from 35 different colleges and universities.

The most common undergraduate major among the class members was biology (including subdisciplines such as genetics, neural sciences, molecular biology, etc.), with 41% the class selecting that as their undergraduate field of study. Science majors taken together accounted for 68% of all majors, while 21% majored in the humanities, 8% majored in the social sciences, and 3% completed independent concentrations. Among the humanities majors, classics, history, music, and philosophy were tied as the most common choices, while health and society was the most popular choice among those majoring in the social sciences. The selection of major among the graduates represents a continuing trend toward a broader range of undergraduate majors, reflecting the larger proportion of postbaccalaureate and PLME students in this class. The postbaccalaureate and PLME students were less likely to be science

majors than were traditional premedical students or the 7-year MEP students.

Where They Are Going

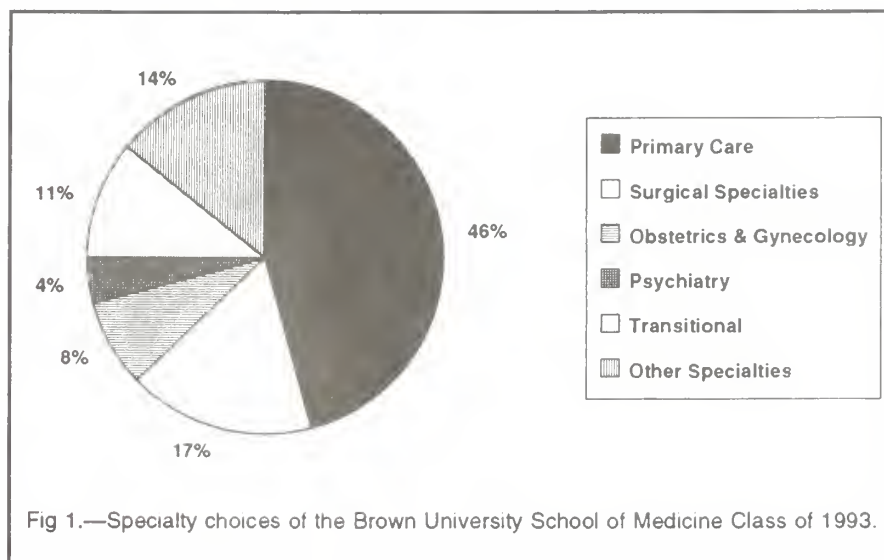
Internal medicine remains the most frequently selected specialty. The proportion of the graduates entering internal medicine is just slightly lower than last year, but remains higher than the low points reached in 1990 and 1991, as shown in Table 2.

The proportion of the class entering specialties in primary care decreased somewhat from the previous banner year. Fewer than half of the graduates entered residency training programs in the primary care fields of internal medicine, pediatrics, or family practice. An unusually small number of graduates going into pediatrics brought the overall primary care figures down this year. Figure 1 illustrates the specialty choices of the Class of 1993.

Table 4 lists all the Class of 1993 graduates and where they will under-

take their residency training. Of the 72 graduates who will enter residency training next year (four are delaying their residencies for 1 year), 15 graduates (21%) matched with Brown-affiliated residency programs and will be staying in the state. Next to Providence, Boston and New Haven seemed to be particularly attractive places for the Class of 1993, with each city receiving five graduates for their 1st year of residency training. The greater Washington, DC area will also have five of our graduates, three of whom will be at the Walter Reed Medical Center. Four graduates each will be in Philadelphia and New York City.

California will be the home for seven graduates next year and ranks second to Rhode Island as the most popular state for residency training. Table 3 lists those states where the graduates will be going for their first year of residency training. As with preceding classes, this class overwhelmingly preferred the Northeast and West Coast to the South and Central states. Nearly two-thirds (65%) will be spending their



first year of residency in the Northeast and one-fifth on the West Coast. In contrast, only five students (7%) will be in the South, and six students (8%) will be in the Central region.

Conclusion

The pattern of career choice of the MD Class of 1993 does not indicate a clear trend in specialty choice. This year's class did not sustain the dramatic rise in primary care interest shown in the previous class, largely due to an uncharacteristically low number of students going into pediatrics. However, this class did not revert to the subspecialty orientation that seemed to be the trend in the late 1980s.

The 1993 results of career choices of Brown graduates closely mirrors what transpired on a national level for all US medical school graduates. Nationally, the number going into family practice residencies increased by 4%, the number remained largely unchanged in internal medicine, and decreased by a little over 1% in pediatrics.¹ Thus, while not deteriorating further, the dearth of graduates entering primary care residency programs does not seem to be improving either. The number of medical school seniors expressing a preference for a career in primary care has fallen from 36.1% to 14.6% within the last decade.²

Brown's medical school has always provided a supportive environment for students interested in primary care and has earned a national reputation for excellence in this area. It is the only Ivy League medical school with a sep-

arate department of family medicine. The medical school has had a required primary care clerkship since its founding. The new dean, Donald Marsh, has reaffirmed Brown's commitment to this tradition. Yet, the effect that medical school curriculums have on career choice pales in comparison to the influence of larger societal and economic forces.³ Perhaps the much awaited plans for health care reform will bring about the changes needed to redress the imbalance.

Acknowledgments

My thanks to Ruth Sauber and Marilyn Doyle in the Office of Medical Student Affairs, Brown University School of Medicine for assistance in summarizing the data.

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Table 3.—State in Which the First Year of Residency Training is Located for the Brown University School of Medicine M.D. Class of 1993

State	No.	(%)
California	7	(9.2)
Connecticut	6	(7.9)
Dist. of Columbia	5	(6.6)
Florida	1	(1.3)
Georgia	2	(2.6)
Hawaii	1	(1.3)
Illinois	1	(1.3)
Maryland	5	(6.6)
Massachusetts	5	(6.6)
Michigan	1	(1.3)
Missouri	1	(1.3)
New Hampshire	1	(1.3)
New Mexico	2	(2.6)
New York	6	(7.9)
North Carolina	1	(1.3)
Ohio	3	(3.9)
Oregon	1	(1.3)
Pennsylvania	4	(5.3)
Rhode Island	15	(19.7)
Texas	1	(1.3)
Washington	3	(3.9)
Delaying Residency	4	(5.3)
Total	76	(99.8)*

* Total does not equal 100 due to rounding

Table 4.—Brown University School of Medicine Class of 1993 Residency Positions

Graduate	Hospital/Medical School Affiliation	Specialty
Ahmad, Nadeem	Barnes Hospital/Washington University School of Medicine	Internal Medicine
Anderson, Richard	Univ Hospitals of Cleveland/Case Western Reserve Univ	Orthopaedics
Ashling, Kerri	Oregon Health Sciences University School of Medicine	Family Medicine
Aurora, Rashmi	North Shore University Hospital/Cornell University	Internal Medicine
Blander, Daniel	Hospital of the University of Pennsylvania/Univ of Penn	Urology
Bond, Andtea	Memorial Hospital of Rhode Island/Brown University	Family Medicine
Boyle, Daniel	Walter Reed Army Hospital/Washington, D.C.	Transitional
Cancro, Carol	Moses H. Cone Memorial Hospital/Univ of North Carolina	Family Medicine
Cekleniak, Natalie	Pennsylvania Hospital/University of Pennsylvania	Obstetrics/Gynecology
Chun, Benjamin	Tripler Army Medical Center/Hawaii	Transitional
Clark, Mark	St. Luke's-Roosevelt Hospital/Columbia University	Emergency Medicine
Coleman, Dwight	Emory University School of Medicine	Psychiatry
Compere, Virginia	Yale-New Haven Hospital/Yale University	Internal Medicine/Prelim
Corrigan, Kathleen	Malden Hospital/Boston University	Family Medicine
Costa, Robert	Roger Williams General Hospital/Brown University	Internal Medicine/Prelim
D'Annunzio, Donald	Roger Williams General Hospital/Brown University	Internal Medicine/Prelim
Etemad, Kambeze	Delaying Residency	
Fish, Heidi	Butler Hospital/Brown University	Psychiatry/Prelim
	Mass. Mental Health Center/Harvard Medical School	Psychiatry
Flanagan, Katherine	St. Luke's-Roosevelt Hospital/Columbia University	Obstetrics/Gynecology
Fortin, Kathleen	The Miriam Hospital/Brown University	Internal Medicine
Friedberg, Marc	Rhode Island Hospital/Brown University	Surgery/Prelim
	New England Medical Center/Tufts University	Neurological Surgery
Garelick, Laura	Franklin Square Hospital/Georgetown University	Family Medicine
Gelzinis, Theresa	Roger Williams General Hospital/Brown University	Internal Medicine/Prelim
	Brigham & Women's Hospital/Harvard Medical School	Anesthesiology
Gendreau, Mark	Dartmouth-Hitchcock Med. Center/Dartmouth Med. School	Surgery/Prelim
Gery, Brian	Walter Reed Army Hospital/Washington, D.C.	Internal Medicine
Greenier, Vanessa	Graduate Hospital/University of Pennsylvania	Internal Medicine/Prelim
	Emory University School of Medicine	Anesthesiology
Greenwald, Nancy	Roger Williams General Hospital/Brown University	Internal Medicine/Prelim
	University of Michigan Hospitals/University of Michigan	Physical Med & Rehab
Henderson, Galen	Rhode Island Hospital/Brown University	Internal Medicine/Prelim
	Longwood Area & Affiliated Hospitals/Harvard Med. School	Neurology
Herring, Lisa	Rush-Presbyterian-St. Luke's/Rush University	Internal Medicine/Prelim
	Emory University Hospital/Emory University	Neurology
Hoy, John	California Pacific Medical Center/Univ. of California-SF	Internal Medicine
Hua, Jenny	Stanford University Hospital/Stanford University	Obstetrics/Gynecology
Huang, Nick	Veterans Affairs Medical Center West LA/Univ of California	Internal Medicine
Johnson, Gregory	Boston University Hospital/Boston University	Internal Medicine
Josefberg, Howard	Yale-New Haven Hospital/Yale University	Internal Medicine/Prelim
	Barnes Hospital/Washington Univ. School of Medicine	Radiation-Oncology
Joyal, Steven	Roger Williams General Hospital/Brown University	Internal Medicine/Prelim
Jung, Alan	University of Washington Affiliated Hospitals/Univ of WA	Medicine-primary
Kornstein, Howard	Mount Auburn Hospital/Harvard Medical School	Internal Medicine
Kuo, David	Yale-New Haven Hospital/Yale University	Medicine-primary
LaFontaine, Paul	Emory University Hospital/Emory University	Surgery/Prelim Emory
	University Hospital/Emory University	Urology
Lando, James	University of New Mexico School of Medicine	Psychiatry
Langlois, Leo	Walter Reed Army Hospital/Washington, D.C.	Neurology
Lasser, Suzanne	Yale-New Haven Hospital/Yale University	Internal Medicine
Lee, Brent	Georgetown University Hospital/Georgetown University	Internal Medicine
Li, Robert	Yale-New Haven Hospital/Yale University	Internal Medicine
Lloyd, Granville	Delaying Residency	
Lombardi, Anthony	Rhode Island Hospital/Brown University	Medicine-primary
Masch, Rachel	Reading Hospital & Medical Center/Temple University	Obstetrics/Gynecology
Medeiros, Brian	Rhode Island Hospital/Brown University	Pediatrics
Medeiros Arfindell, Carroll	Brigham & Women's Hospital/Harvard Medical School	Obstetrics/Gynecology
Montgomery, John	Naval Hospital/Jacksonville, FL	Family Medicine
Osborne, Olive	Westchester Cty Med. Center/New York Medical College	Internal Medicine/Prelim
	Kings Cty Hospital Center/SUNY Hlth Sci Ctr at Brooklyn	Ophthalmology

Table 4.—Brown University School of Medicine Class of 1993 Residency Positions, Continued

Graduate	Hospital/Medical School Affiliation	Specialty
Pacheco, Paulo	The New York Hospital/Cornell University	Internal Medicine
Perepelyuk, Evelina	Sinai Hospital of Baltimore/Johns Hopkins University	Obstetrics/Gynecology
Pierce, Robert	University of Washington Affiliated Hospitals/Univ of WA	Pathology
Ramratnam, Bharat	The Miriam Hospital/Brown University	Internal Medicine
Real, Diane	Rhode Island Hospital/Brown University	Internal Medicine/Prelim
Rossi, Humberto	Francis Scott Key Medical Center/Johns Hopkins Univ.	Medicine-Primary
Salgado, Arturo	LAC-USC Medical Center/Univ. of Southern California	Emergency Medicine
Singh, Navin	Johns Hopkins Hospital/Johns Hopkins University	Plastic Surgery
Soldes, Oliver	University of Michigan Hospitals/University of Michigan	Surgery
Staebler, Michael	Rhode Island Hospital/Brown University	Orthopaedics
Swartzman, Julie	Georgetown University Hospital/Georgetown University	Internal Medicine
Sweeney, Tara	Norwalk Hospital/Yale University	Internal Medicine/Prelim
	Manhattan Eye, Ear and Throat Hospital/Cornell Univ.	Ophthalmology
Tabatabai, Mehra	John Peter Smith Hospital/Univ. of Texas Southwestern	Orthopaedics
Tallo, Christopher	University of Cincinnati Hospital/University of Cincinnati	Pediatrics
Telfeian, Albert	Delaying Residency	
Ting, Chiapone (David)	Sinai Hospital of Baltimore/Johns Hopkins University	Internal Medicine
Townsend, Kimberley	University of Cincinnati Hospital/University of Cincinnati	Pediatrics
Valentini, Robert	Delaying Residency	
Ward, Alison	Madigan Army Medical Center/Tacoma, WA	Pediatrics
Weber, Philip	Mount Sinai Medical Center/Mt. Sinai School of Medicine	Surgery/Prelim
Welsh, John	Stanford University Hospital/Stanford University	Internal Medicine
Winston, Rebecca	University of New Mexico School of Medicine	Family Medicine
Yoon, Min	Boston University Hospital/Boston University	Surgery/Prelim
	Boston University Hospital/Boston University	Otolaryngology
Yuan, Jessie	Community Hospital-Santa Rosa/Univ. of California-SF	Family Medicine
Zaslow, Jay	Community Hospital-Santa Rosa/Univ. of California-SF	Family Medicine

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The "Reading" of Patients

Lynn C. Epstein, MD

... medical education has been grappling with methodological approaches that help to foster patterns of "lifelong learning," thereby enabling graduates to modify and update their knowledge base.

The Report of the Project Panel on the General Professional Education of the Physician (GPEP) and educational and specialty groups have renewed the emphasis given to the doctor-patient relationships.¹⁻³ A basic element in the call for more humanism is that doctors should treat their "patients" as "real people." This tenet asks that doctors learn enough about their patients to understand the ramifications that their illnesses have on their lives. Medical professionalism is enhanced by this empathetic framing of illness within the patient's life.

The informational base of medicine threatens to overwhelm medical students with "facts" to the possible detriment of their abilities to "care" for patients.^{1,3,4} Moreover, the "facts" of medical education, like other forms of information, do not remain static. Rather, much of what medical students are taught today will be quickly outdated, requiring continual and active revision over the course of their professional careers. Accordingly, medical education has been grappling with methodological approaches that help to foster patterns of "lifelong learning," thereby enabling graduates to update their knowledge. The trend toward active-learning teaching strategies in medical schools is one example of the increasing emphasis on cultivating appropriate attitudes and interactions while acquiring the requisite grounding.

The combination of the above two directions has contributed to a general rethinking of how to approach medical education. Hence, both the content

and the process of acquiring the essential knowledge, skills, and attitudes have undergone serious reconsideration. One element in the revamping of the educational continuum is the development of medical "humanities" courses, to help students become complete physicians (eg, human values in medicine, medical ethics, and literature and medicine courses).

This paper will introduce one of the medical humanities approaches receiving notice and attention in several medical school curricula today, Literature and Medicine. Through a brief look at an interdisciplinary collaboration with (and a tribute to) Professor Harriet W. Sheridan, dean emerita (July 21, 1925-September 8, 1992) at Brown University, this article will explore the "and" in Literature and Medicine.

Overview

There has been a re-discovery of the relevance of literature to medical education.^{5,6} In part, this is a rededication of medicine as a noble profession. Or as Osler put it, "'Tis no idle challenge which we physicians throw out to the world when we claim that our mission is of the highest and of the noblest kind . . ."⁷

Although images of illness and of healers abound in literary texts, the systematic study of these themes is comparatively recent. The analysis of print text enables medical students to view the role of the physician from the "other side." When dealing with patients and their families, students are apt to be focused on the technical medical aspects of what they are doing to the detriment of appreciating the personal impact on those directly involved. However, as a reader, it is easier for the student to identify with the issues of being a patient, how the illness unfolds and is experienced, as

well as the peculiarities of the medical system. Compelling questions about doctor-patient relationships and medical treatment emanate from literary works. Medical science seems less "certain" when examined through the realm of historic works that sometimes reveal adherence by doctors to flawed dogma. For many physicians, literature about medicine provides a comfortable venue to expand their understanding of their patients and themselves.

The author's joint endeavor into literature and medicine with Professor Sheridan began after we became involved together in faculty development programs. Sharing a firm commitment to active student participation in the learning process, (which she called collaborative learning and I referred to as problem-based learning), we ventured into each other's domains. Then, when I attempted to involve her in our medical program, she instead recruited me to co-teach the literature and medicine course with her for a carefully chosen mix of undergraduates and graduate students (medical and non-medical). The seminar course, begun together in 1991 and which I now continue, The Doctor: Subject and Author, combines analysis of the rhetorical and thematic aspects of texts to further students' understanding of the doctor/patient relationship. It was Harriet's firm conviction that it should not be necessary for a physician to be sick to understand what the experience of illness means.

We agreed with Norman Cousins when he wrote, "Literature helps the medical student to analogize the pa-

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ABBREVIATIONS USED:
GPEP: General Professional
Education of the Physician
RWJ: Robert Wood Johnson
(Foundation)

tient, to make connections between the experiences of the race and the condition of the individual, and to fit the individual into a world that is not as congenial as it ought to be for people who are more fragile than they ought to be."⁶ To this end, students read a variety of works in different genres about doctors and by doctors (by such authors as Chaucer, Moliere, G.B. Shaw, Tennessee Williams, Sir Thomas Browne, Keats, William Carlos Williams, Oliver Sachs, and so on).

Using a collaborative learning format, the course addressed such questions as: Is the literary image of the doctor represented in a consistent pattern from age to age and text to text?

Conducted using a collaborative learning format, the course addressed such questions as: Is the literary image of the doctor represented in a consistent pattern from age to age and text to text? Has it taken on a symbolic identity? Are texts written by doctors marked by evidences of medical training in their rhetorical choices apart from subject matter? Are there literary concepts or modes (biography, narrative form, metaphor, etc.) that have been particularly adaptable to doctors' writings? What are the themes of such writings? Can the texts of doctors who are writing about themselves as patients be characterized in any specialized rhetorical way? Many other questions developed from class discussion including: the experience of illness, the tools of healing, the complexities of the profession, coming to grips with mortality, the limits of knowledge, issues of race, class and gender, morals, ethics, societal priorities, etc.

The course included students following different academic pathways: premedical students, those concentrating in English, history or other social sciences, as well as 4th year medical students and English graduate students. Classroom discussions and analyses of texts reflected these disparate starting points. For some students, the con-

tent, message or persona was the focal point for interpretations, while for others, it was the form and structure of the text that was scrutinized. This attention to the two aspects, the "medicine" on one hand or the "literature" on the other, invariably led someone to raise the question anew of whether the concern was with medical narratives per se or with literary texts centering on medical subjects. Then the task became one of exploring the interaction between the two scholarly endeavors, indeed partially merging them to find the overlap between them.

How can we then define the "and" linking literature to medicine? On one level, the combination alludes to the bi-directional nature of the contributions each field makes to the other. Certainly, investigating the portrayal of medical issues through literature provides a vehicle to think about themes that might not have been raised otherwise. Similarly, literary texts provide an alternative to reality and a graphic way to see how medicine is generally perceived. On another plane, the conjunction of literature and medicine is more than the representation of the role of the doctor and perceptions and self-perception of what transpires. Rather, it is a mirror of the process of "doctoring," which helps to define the *modus operandi*.

Each patient has an individual story or narrative, which is more than just their medical history, and which is crucial for the doctor to elicit. Only in this fashion can a doctor truly appreciate the experience of illness for the person and help delineate treatment goals uniquely suited to meet that person's needs. Accordingly, doctors need to learn to identify the subtleties of a patient's story: what is being said, as well as what is left unsaid. It is in this sense, that the concept of the illness narrative expands to encompass the *patient's* story, and the "reading" of patients to mean close attention to understanding the *patient*, rather than just the disease or the illness that accompanies it.^{8,9} Otherwise one runs the risk of "curing the disease and killing the patient," figuratively if not literally.¹⁰

Is literature and medicine itself actually a field or discipline? An entire volume of *Literature and Medicine*, the 10th anniversary retrospective,

addresses the question.¹¹ While an investigation of the topic is beyond the scope of this paper, suffice it to say that no simple answer has emerged. Rather, the importance of open collaboration and dialogue between scholars in medicine and in literature has been stressed.¹² It is certainly not as straightforward to many as to Somerset Maugham, who professed, "I do not know a better training for a writer than to spend some years in the medical profession."¹³

Perhaps the overlap between the two fields is most clearly seen in the specific: the actual tale or story, be it a certain medical case or literary account. In each instance, the vagaries of the "general" are replaced by the details that mark the narrative for the individual. It is largely the response to illness, which varies greatly among people, (or in some instances the lack of one), that makes the narrative real.

... investigating the portrayal of medical issues through literature provides a vehicle to think about themes that would not necessarily have otherwise been raised.

One source for these narratives, which explore the congruence of the literary with the medical, is the book *On Doctoring*, published by The Robert Wood Johnson Foundation.¹⁴ Edited by Dr Richard Reynolds, executive vice president of the foundation, and Dr John Stone, the book brings together stories, poems and essays about doctors, patients and illness to elucidate the "human" side of medicine. First published in 1991, the foundation has since been giving it away free to every 1st year medical student in the country. The existence of this collection, as well as its free distribution to medical students, serves as a testimony to the importance of *literature and medicine* as a way of helping doctors to understand more fully the meaning of illness for patients, their families and for health care providers.

We are all familiar with C.P. Snow's delineation of the forces that have contributed to the separation of the humanities and the sciences into "two cultures" to the mutual detriment of

both.¹⁵ Odegaard builds on Snow's discussion in his essay "Dear Doctor: A Personal Letter to a Physician," and strongly advocates closer ties between the two.⁴ For as C.P. Snow pointed out, while writing about the wisdom of doctors: "I want to suggest to you that they [the doctors] would have been a shade wiser with the elements of a humanistic education. You can't teach wisdom. . . . Yet, if the potentiality of empathy exists in anyone, then it can be encouraged by those who have possessed it and have tried to express it in words. That is why I am inclined to think that there ought to be a literary component throughout the course of medical education."¹⁶

The Harriet W. Sheridan Literature and Medicine Lectureship, Brown University

Illness is a very democratic process, cutting across all sociodemographic lines. Yet the experience of grappling with illness is a uniquely personal one. When confronted with an imminently fatal illness, Harriet went on about her active life, pausing only as absolutely necessary from time to time for treatment. Although she stepped down as dean of Brown, she continued her academic activities, building a Center for the Advancement of College Teaching. In a parallel fashion, interactions with "Doctors" and "Doctoring" helped to stimulate her staunch commitment to medical education. It will come as no surprise to those who knew her that Harriet Sheridan was an astute "medical educator."

April 28, 1993, marked the inauguration of the Harriet W. Sheridan Literature and Medicine Lectureship at Brown University. John Stone, MD, essayist and poet, professor of cardiology and associate dean of medicine at Emory University, was the featured speaker. The 1993 lecture, sponsored by the Francis Wayland Collegium for Liberal Learning, the Center for the Advancement of College Teaching, the Brown University School of Medicine, and the Department of English pays tribute to one aspect of the contributions of a singular individual.

In the future, it is anticipated that

the Harriet W. Sheridan Lecture will continue to address the confluence of literature and medicine and to focus on the analogies between the close reading of print texts and the "reading" of patients. In 1994, the second lecture in honor of Harriet W. Sheridan's interest in literature and medicine, will approach the topic from the literary domain, and will be given by a respected, senior scholar in this emerging field. Beginning with images of illness in print text, it is anticipated that the lecturer will foster a dialogue that expands to include the historical, sociological, anthropological, psychological, economic, ethical, policy, etc., domains.

In the spirit of expanding the margins, the Harriet W. Sheridan Lectureship centers on the "and" of literature and medicine, providing a special forum for interdisciplinary exploration of doctors, doctoring, illness, and healing in literature. It seems particularly appropriate to have this lectureship in Harriet Sheridan's honor, since she argued so cogently for the relevance of literature in medical education and helped to carve it a niche. Moreover, Brown, with its tradition of a "liberal education" in both the college and the medical school, is an especially likely home for this lectureship.

The sponsors of the 1993 lecture are pursuing avenues to raise funds for future lectures.

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The Status of Women in Medicine at the Brown University School of Medicine

Debra B. Abeshaus, BS
Lynn C. Epstein, MD
Agnes B. Kane, MD, PhD
Lois A. Monteiro, PhD

... the number of women faculty has increased over the past decade. Between 1978 and 1988, the percent of women medical school faculty in this nation rose from 15% to 19%, reach 21.5% in 1992.

Given the national surge of women selecting medicine as a career, where do women stand at the Brown University School of Medicine? The increasing number of women entering the medical profession during the past few decades in the US is clearly reflected in the enrollment of female students at Brown, where women have comprised on average 45% of the entering classes in the School of Medicine over the last 5 years.¹ In the Brown University Program in Liberal Medical Education, (the PLME, an 8-year combined degree program leading to both the bachelor's and MD degree), women have accounted for about 49% of all entrants since 1988.² The percentage of females among 1st-year students in the School of Medicine and PLME in fall 1992, was 52% and 55%, respectively.

Similarly, the number of women faculty in medicine has increased during the past decade. From 1978 to 1988, the proportion of women medical school faculty in this nation rose from 15% to 19%,³ reaching 21.5% in 1992.⁴ In February 1993, there were 69 full-time women medical faculty (19.8%, excluding research faculty) at the Brown University School of Medicine, a 6% increase from 1987 to 1993 (see Tables 1 and 2).⁵ While numbers of women medical faculty continue to increase both at Brown and at other medical schools, women tend to be clustered at the rank of

assistant professor (50.2% national average in 1992).^{4,6} At Brown-affiliated hospitals, women physicians currently represent 37% of housestaff officers and 27% of chief residents.⁵ Nationally, the proportion of women among residents was 29.5% in 1990.⁴

The Office of Women in Medicine

In April 1991, Dean David S. Greer established an Office of Women in Medicine at the Brown University School of Medicine, one of only eight US medical schools that has an office dedicated to the advancement of women students, residents and medical faculty. The Office of Women in Medicine evolved from the efforts of the Association of Women Medical Faculty, an affiliate since 1986 of the University Faculty Committee on the Status of Women at Brown. The association encompasses all women medical faculty who hold full time academic appointments or voluntary, clinical appointments (campus or hospital-based, and those in private or group practice), and promotes collaboration, networking, recruitment and the academic advancement of junior medical faculty.

The primary and long term goals of the Office of Women in Medicine at Brown include: creating programs to maximize faculty recruitment, development, advancement, networking and research; working with the women medical student organization, Women in Medicine (WIM), to address the special need for mentors and educational programs; working with the associate dean of medicine for medical faculty affairs to develop mechanisms for adequately addressing gender issues related to faculty and research in the School of Medicine; stimulating recognition of the relatively new NIH

guidelines for women in research (ie, assure inclusion of women in protocols and facilitate research on women's diseases/issues); and expanding educational programs to address gender differences in providers as well as patients in health care delivery (ie, gender issues from the patient's perspective of illness, gender issues in approaching patients, and increasing medical student exposure to clinical settings with female physicians.)

The Office of Women in Medicine (OWM) is administered by the director and the associate dean (LCE) in the coordinating committee of the Association of Women Medical Faculty at Brown. The office and the association work cooperatively to bring together women in medicine at all levels (ie, faculty, students, administrators, housestaff at affiliated hospitals, and women physicians in the community), jointly sponsoring events throughout the academic year. A quarterly newsletter informs and links the local women in medicine constituencies and lists faculty position announcements at affiliated hospitals.

OWM programs have included guest speakers Dr Lois Monteiro, associate dean of medicine for faculty affairs and Professor of Community Health, who spoke on *Research on Health Care Issues for Women*, and Dr Barbara DeBuono, Clinical Assistant Professor of Medicine and Direc-

Ms Abeshaus is director, Office of Women in Medicine and PLME student affairs; Dr Epstein is associate dean of medicine, clinical associate professor of community health and currently president of RIMWA; Dr Kane is associate professor of pathology; and Dr Monteiro is associate dean of medicine and professor and chair of community health; all are at Brown University School of Medicine.

ABBREVIATIONS USED:
NIH: National Institutes of Health
ORWH: Office of Research on Women's Health
OWM: Office of Women in Medicine
PLME: Program in Liberal Medical Education
RIMWA: Rhode Island Medical Women's Association
WIM: Women in Medicine

tor of the Rhode Island Department of Health. Dr DeBuono addressed her role as director and discussed health care issues and goals regarding the status of women's health in Rhode Island. Other presentations sponsored or co-sponsored by the OWM have included *Aging 2000 of Rhode Island* by Dr Marsha Fretwell, medical director of Aging 2000; *A Curriculum in Women's Health* by Dr Jeanne Arnold, AMWA's national director of students; and a panel presentation on *Women of Color in Medicine*.

More recently, the OWM, the Sciences Library and the John Hay Library at Brown University co-sponsored an exhibition, *Women in Health Care Through the Ages*, in honor of Women's History Month in March 1993. Also in March, Dr Vivian Pinn, director of the Office of Research on Women's Health (ORWH) of the National Institutes of Health (NIH), visited the School of Medicine, and informed Brown medical faculty and students of her office's mandates and new programs. The ORWH aims to: (1) identify gaps in knowledge related to women's health research, and ensure that research efforts at NIH address those gaps in knowledge; (2) monitor and ensure that women are included in clinical trials; and (3) foster the recruitment and advancement of women in biomedical careers.⁷

The OWM and the association also offer programs that center on academic advancement for junior faculty. A *Faculty Development Workshop for Women Medical Faculty, Fellows and Residents at the Brown University School of Medicine*, held in April 1993, provided participants with opportunities to identify and learn skills required for professional development in academic medicine in the areas of innovative teaching, leadership, advancing an independent research program and obtaining research funding. Individual breakout sessions were held on *Innovations in Education, Clinical Research-Grants, Leadership and Management Skills, Basic Science Research-Grants, Clinical Research, and Interdisciplinary Research*.

The Mentor Program

A Women in Medicine Mentor Program, initiated in 1988, matches wom-

en medical students with women medical faculty, and with physicians in the community who are members of the Rhode Island Medical Women's Association (RIMWA). Mentoring presents students with role models, support and possibilities for early career exploration, networking and clarification of goals. At many institutions, women are frequently unaware of the value of mentoring in professional development and do not seek out appropriate supports.⁸ To expand mentoring relationships for women medical students at Brown, students are invited to express their interests in spending time with a physician from a particular medical specialty, subspecialty, or area of specialized health care delivery (eg, primary care, public health, rural medicine, international health, and women's health care). Others may decide to meet with a physician to discuss such specific issues as combining a career in biomedical research and clinical practice; balancing professional and family responsibilities; pursuing an advanced degree as the MPH; and discussing opportunities for residency training. Some students elect to meet with a mentor for a few times to acquire a better understanding of a medical specialty, while others choose to continue their relationship for a longer period. In looking ahead towards extending the program to all students, both female and male, we plan to develop early clinical experiences that will address gender issues in health care delivery.

There is an active women's medical student organization, "Women in Medicine" or "WIM," at the Brown University School of Medicine. WIM has three co-leaders who work with other students to plan informative events pertinent to women pursuing careers in medicine. The group's programs highlight issues related to women as health care providers and women as patients. A sampling of forums and seminars sponsored by WIM have included *Practice Options for Women: Opportunities and Obstacles*; *Physician Response in Sexual Assault Cases*; *Women's Health Care Issues Discussed by Women Researchers*; *Career and Family: Can You Have It All?*; and *Domestic Violence: Recognizing Signs & Responding*.

The OWM, acknowledging the

many constituencies addressing issues for women in the profession, has reached out to and networked with the larger Rhode Island community. The director (OWM) serves as the liaison to the Rhode Island Medical Women's Association (RIMWA) for Brown medical students. The two organizations, OWM and RIMWA, have co-sponsored several programs for women students and physicians. Many RIMWA members have volunteered to serve as mentors, thereby providing student access to a variety of clinical sites. More recently, RIMWA and the OWM have joined in surveying and bringing together women residents from Brown affiliated hospitals. Similar collaboration with the Rhode Island Commission on Women and other women's groups has helped to strengthen the network for all.

Summary

Although the number of women medical faculty appointed and promoted at the School of Medicine has increased gradually since 1987, the extent to which women have advanced in academic medicine and the timeliness of their movement forward are of concern. With women constituting nearly 20% of the medical faculty at Brown, and comprising only 5% of professorial appointments, it is easy to see the disparities. While the Brown University School of Medicine stands out as one of less than a dozen medical schools with an Office of Women in Medicine, clearly there is still much to accomplish in this domain. Progress may be accelerated through networking and advocacy promoted by professional development programs sponsored by offices for women in medicine and organizations as RIMWA. Offering women medical faculty a forum to discuss issues as departmental promotion criteria in academic medicine and to link up with other women physicians, ultimately serves not only women faculty but their institution. Providing role models is critical to assist women medical students in looking well ahead to plan for their own career development. In creating opportunities for dialogue among women in medicine at all levels in the medical school environment and among women physicians in the near-

by community, institutions take an essential step forward towards supporting women's advancement in medicine.

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Necrology 1992 Addendum

Mark A. Yessian

Dr Mark A Yessian, 86, of Warwick, died Jan. 4, 1992 at home. He was the husband of Hasmig Jane (Tufenkjian) Yessian. Born in Pawtucket, he was a son of the late Atche and Agnes (Barsamian) Yessian.

Dr Yessian was a graduate of Providence College in 1928 and received his medical degree from Hahnemann Medical College, Philadelphia, in 1932. He served his internship in hospitals in Philadelphia and at the former Charles V. Chapin Hospital, Providence. He served as a captain in the Army Medical Corps in the Asiatic-Pacific Theater for 4 years during World War II. After discharge he did post-graduate work in internal medicine and cardiology at Harvard Medical School before returning to practice in Providence.

He was a member of the staffs at Roger Williams Hospital and Rhode Island Hospital and had been a consultant in internal medicine for 10 years at the former State Infirmary, Cranston. From 1963 to 1982 he was clinical director at the Rhode Island Medical Center, Cranston. He was a past president of the medical staff at Roger Williams Hospital and had formerly served on the board of trustees at the Rhode Island Heart Association. He was a member of the Providence Medical Association, the Rhode Island Medical Society, the Internal Medicine Society of Rhode Island, and was an active member of the AMA. He was a member of St Sahag & St Mesrob Armenian Apostolic Church, Providence.

Besides his wife he leaves a son, Dr Mark R. Yessian of Boston; a daughter, Linda J. Cameron of Warwick; two sisters, Sophie Kasparian of Warwick and Sarah Asadorian of Cranston; and two grandchildren.

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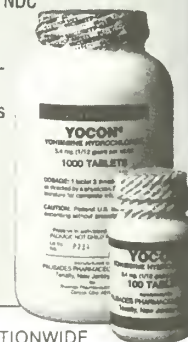
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

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Table 1.—Brown Medical School Faculty by Sex and Rank: January, 1987

Women	52 Total Rank	No.	% of Women
	Professor	1	1.9
	Associate Professor	11	21.2
	Assistant Professor	20	38.5
	Instructor	4	7.7
	Research	16	30.8
Men	259 Total Rank	No.	% of Men
	Professor	74	28.6
	Associate Professor	54	20.8
	Assistant Professor	86	33.2
	Instructor	14	5.4
	Research	31	12.0

Percent of total faculty at each rank by gender		
Rank	Women	Men
Professor	1.3	98.7
Associate Professor	16.9	83.1
Assistant Professor	18.9	81.1
Instructor	22.2	77.8
Research	34.0	66.0

Full-time Medical Faculty (minus research faculty)			
Men	228/264	=	86.4%
Women	36/264	=	13.6%

Source: Office of Faculty Affairs Database Brown University School of Medicine

Table 2.—Brown Medical School Faculty by Sex and Rank: February, 1993

Women	92 Total Rank	No.	% of Women
	Professor	5	5.4
	Associate Professor	17	18.5
	Assistant Professor	44	47.8
	Instructor	3	3.3
	Research	23	25.0
Men	323 Total Rank	No.	% of Men
	Professor	95	29.4
	Associate Professor	76	23.5
	Assistant Professor	98	30.3
	Instructor	10	3.1
	Research	44	13.6

Percent of total faculty at each rank by gender		
Rank	Women	Men
Professor	5.0	95.0
Associate Professor	18.3	81.7
Assistant Professor	31.0	69.0
Instructor	23.0	77.0
Research	34.3	65.7

Full-time Medical Faculty (minus research faculty)			
Men	279/348	=	80.2%
Women	69/348	=	19.8%

Source: Office of Faculty Affairs Database Brown University School of Medicine

Resident Physician Abstracts: Annual Scientific Meeting of the Rhode Island Chapter of the American College of Physicians

Fred J. Schiffman, MD

The Seventh Annual Joint Meeting of the Rhode Island Chapter of the American College of Physicians (ACP) and the Department of Medicine of Brown University was held at the Omni Biltmore Hotel on Tuesday and Wednesday, March 9 and 10.

This year the presentation of residents' and fellows' abstracts was begun Tuesday evening and posters continued to be displayed during the session on Wednesday.

There were 67 posters presented with the vast majority representing work of resident physicians and faculty from all Brown-affiliated hospitals. This year there were 30 more posters than at last year's session, and dedicating an evening for their presentation and review with wine, cheese and hors d'oeuvres in the ballroom foyer on the 17th floor of the Omni Biltmore Hotel was an important and pleasant change from last year.

There were 17 oral presentations in three separate sessions during Wednesday morning and afternoon. Most of these represented more than clinical vignettes. Clinical studies involving multiple patients and institutions and exhaustive literature reviews as well as bench research were common themes for these presentations. (The 17 orally presented abstracts are included at the end of this article).

There was a panel discussion moderated by Joseph A. Chazan, MD, FACP, governor of the American College of Physicians of Rhode Island. Richard Carleton, MD, FACP, Physician-in-Chief at Memorial Hospital of Rhode Island, presented a work on preventive care in Pawtucket's Heart Program. Alvin L. Schultz, MD, FACP, (the official ACP representa-

tive), discussed cost-effective use of thyroid function tests and Michael Barry, MD, FACP, of Massachusetts General Hospital, spoke on the early diagnosis of prostate cancer. A luncheon followed this panel discussion and Dr Alvin L. Schultz discussed news from the ACP.

The Irving A. Beck Award, (named for Irving A. Beck, MD, an eminent Rhode Island physician and member of the American College of Physicians), is presented annually at this meeting to an outstanding internist and member of the ACP/Rhode Island Chapter, for long and sustained career service to patients. This year, Constantine S. Georas, MD, FACP, was the recipient of this award. He is an internist and cardiologist who has practiced medicine in Rhode Island since 1958. Dr Georas received his education in Greece and his medical degree from the University of Athens. He then interned and spent 1 year in residency at the Hospital for Joint Diseases in New York. From there he completed his residency and subsequently did his cardiology fellowship at Rhode Island Hospital.

Dr Georas is a physician and cardiologist at the Rhode Island Hospital and assistant clinical professor of medicine at Brown Medical School. He is a Diplomate of the American Board of Internal Medicine in cardiovascular diseases, a fellow of the American College of Cardiology and a fellow of the American College of Physicians.

This year, once again, no prizes were awarded for selected presentations. However, all presenters were honored in the form of beautiful wooden plaques for those who presented orally and calligraphed certificates for poster presenters. All participants also received a full year's membership in the American College of Physicians, which includes a subscription to the

Annals of Internal Medicine.

This year, as in the past, the quality of the presentations was outstanding and reflected the ongoing concerns of members of the Brown University Medicine faculty, both hospital and office-based, who serve as mentors and guides for physicians in training throughout the Brown system.

Oral Presentations

1. Outcome of Septic Arthritis in Adults.

Peter Martens, MD (Associate) and George Ho, Jr, MD, FACP.

A review of adults with septic arthritis (SA) was undertaken to evaluate outcome of treatment in a community-based teaching hospital.

During an 80-month period (1986-1992), 38 cases of SA were identified. Underlying joint disease was present in 84% of cases. Mean age was 68 yrs with a range of 26 to 100 and a median of 70. Patients did not always initially display signs of infection; fever was present in only 42% and leukocytosis in 67%. Total in-hospital mortality was 26%, but the mortality attributable to SA was 13%. Polyarticular SA occurred in 26% of cases and carried a 40% mortality. Twenty-four percent of cases required transfer to the intensive care unit (ICU); they had a 67% mortality. Three of the 4 patients with polyarticular SA requiring ICU care died.

Average length of hospital stay for survivors receiving a full course of antibiotics (19 patients) was 35 days; it diminished to 14 days for 5 uncomplicated cases who received home IV antibiotics. Eighty-nine percent of survivors had return of function of the affected joints. Twenty-one percent required surgical intervention and 5% were complicated by osteomyelitis.

SA remains a costly disease affecting primarily the elderly with underlying joint disease. Polyarticular SA and the need for ICU care portend a high mortality. The function-

Fred J. Schiffman, MD is associate professor of medicine, Brown University School of Medicine, Providence RI.

<p>ABBREVIATIONS USED ACP: American College of Physicians FACP: Fellow of the American College of Physicians</p>

al outcome of those who recovered was generally good.

2. Association of Cholesterosis and Pancreatitis.

Hal Buch MD, John Welsh and Amer Malik, MD

Acute idiopathic pancreatitis (AIP) is a significant clinical problem. The incidence of AIP is 9% to 39% with a relatively high overall mortality of 10% to 25%.

It has been suggested that patients with recurrent attacks of AIP must be considered at a high risk of having gallbladder cholesterosis. It has been postulated that the etiology of the correlation between gallbladder cholesterosis (GBC) and AIP is temporary impaction of cholesterosis polyps at the sphincter of Oddi. Paricio et al (*Br J Surg*. 77:735-736) have suggested that all patients with recurrent AIP be considered for cholecystectomy as they found 49% of their patients with GBC but without gallstones developed recurrent AIP.

A retrospective review of 4293 cholecystectomies was performed to investigate the relationship between gallbladder cholesterosis and acute pancreatitis. There were 21 cases of pancreatitis for an overall incidence of 0.49%. All cases of pancreatitis were associated with cholesterosis. Out of 263 cases of cholesterosis, 80 did not have any gallstones. Of the patients with cholesterosis but no gallstones, four were found to have pancreatitis (recurrent in all). Intraoperative cholangiograms at time of cholecystectomy in all four were negative. None of these patients had cholesterol polyps in their gallbladders. All were of the planar (flat) variety. Follow up (range 61 to 86 months) showed no further attacks of pancreatitis in three patients. One patient could not be contacted.

All cases of pancreatitis were associated with cholesterosis. Since the 4 patients with GBC and AIP lacked cholesterol polyps as well as gallstones, we, therefore, postulate that cholesterosis may simply be an indicator of a high propensity to form microlithiasis. Gallbladder cholesterosis can lead to pancreatitis. Removing the gallbladder is indicated to prevent further attacks of pancreatitis only in the subset with evidence of cholesterosis.

3. The Post Admission Hemoglobin Drop: Myth or Reality?

Aaron Richman, MD, and Philip O'Dowd, MD

It is entrenched in housestaff lore that hospitalized patients will drop their hemoglobin 1 gram within 24 hours of admission and that this drop does not warrant an investigation for bleeding or hemolysis. The phenomenon is usually attributed to hydration and/or phlebotomy.

We designed a small study to test the validity of this "rule." We sought to determine whether there was a drop in hemoglo-

bin, to determine the magnitude of the drop if present and to correlate the hemoglobin change with in-hospital hydration.

Medical patients were included if: (1) There were Hgb values at the time of admission and on the morning after admission; (2) There was no known bleeding; and (3) There was no transfusion of packed red blood cells.

Data collected included: (1) The Hgb values; (2) IV fluids given (an approximation of hydration since PO fluids, IV medications and other potential fluid balance variables were not considered); and (3) BUN/Cr values.

The results confirm the validity of the rule of thumb. Forty-four of 48 (92%) of the patients experienced a drop in Hgb. The Hgb changes ranged from +0.6 gm % to -4.5 gm % with a mean of -1.15 gm % and a median of -1.10 gm %.

Plots of DHgb vs. IV hydration and DHgb vs BUN suggest that although hydration plays a significant role other factors must also play a role. Candidates include posture, stress, exercise/muscular activity, phlebotomy, and diurnal variation. We will present the graphical data and review the literature with respect to these "secondary" factors.

4. Lymphocytopenia, A Common Admission Finding

Rohit Malhotra, MD, and Philip O'Dowd, MD

Among the various cytopenias that draw housestaff attention, lymphocytopenia (LP) is a neglected finding. This is not surprising. While the major textbooks of hematology have chapters on the differential diagnosis and mechanisms of neutropenia, most neglect LP altogether. The subject receives little attention in the clinical journals as well. The most cited clinical article, a vintage 1971 study, documents that "lymphocytopenia occurred in 2.4% of 7350 Mayo clinic patients" and emphasized "the rarity of lymphocytopenia."

It was our impression that LP was a frequent occurrence, and we set about to document the incidence of LP in RWMC admissions. We reviewed records of 251 consecutive medical admissions. Patients were excluded if a CBC with differential was not available at admission. Although Wintrobe's *Textbook of Hematology* defines LP as a total lymphocyte count (TLC) <1500/cu mm, we applied the more stringent definition requiring TLC <1000/cu mm and classified patients with TLC <500/cu mm as severely lymphocytopenic.

Even by the stringent definition, LP was present in one-third of admissions (79/251=32%) with 1 of 10 admissions qualifying as severe LP (22/251=9%).

Contrary to the literature, LP is a common finding at admission to a medical service. Only a few of these patients were on steroids (6/79), had received recent chemotherapy/radiation therapy (11/79) or were HIV-in-

fectected (0/79), the commonly cited causes of LP. We found that an infectious presentation was the condition most associated with LP, accounting for 22% (17/79) of all lymphocytopenic patients and 45% (10/22) of those with severe LP. LP is apparently not a specific finding, however, since coronary artery disease (8/79) and untreated malignancy (6/79) were among the major diagnostic categories. The LP was often transient, resolving within days of admission and therapy. We review the diagnoses and medications of the lymphocytopenic patients and speculate as to the cause of this common finding.

5. Subjective Reporting of Cancer Pain as a Determinant of Subsequent Pain Management in Elderly Hospice Patients

Wendy M. Stein, MD and Ralph P. Miech, MD, PhD

Is there a correlation between subjective pain assessment and other clinical variables in geriatric hospice patients with cancer?

This was a retrospective record review and observation of home visits from a community-based hospice covering the state of Rhode Island.

From a sample of 537 patients with terminal cancer admitted to hospice during 1990, 239 patients 65 years of age and older were identified retrospectively.

Of the 239 patients, 89% survived 90 days or less with 21% living 7 days or less. Upon admission, 55% of the total sample subjectively reported some pain, with 44% reporting pain in the range of discomfort to excruciating. Of those patients not reporting pain upon admission, 55% went on to experience pain, requiring subsequent pain management. There was no relationship between the patient's reporting of pain on admission and subsequent survival time. Also, there was no relationship between the length of time from initial diagnosis to hospice admission and the patient's subjective reporting of pain intensity; likewise, using a younger group of terminally ill cancer patients for comparison in these same areas, there were no significant differences found accounted for by age. Specifically, there were no statistically significant differences between under and over age 65 groups in terms of survival after admission and in terms of level of pain intensity subjectively reported upon admission. There was a difference between the admission nurse's placement of pain on the problem list and the patient's subjective reporting of pain. Although the numbers were extremely small, it was found that a nurse was almost twice as likely to incorrectly leave off pain from a problem list as s/he was to incorrectly ascribe pain to a patient not subjectively reporting pain at the time of the interview. This was not true in the younger comparison group. For patients entering hospice with pain symptomatology, early concentration of pain management services is crucial. For patients

entering hospice without pain, attention to initial onset of pain requires both appropriate assessment and specific treatment plans to minimize suffering.

6. The Regulation of HIV-1 Gene Expression by the TAT Protein

Michael Newstein, Im-Soon Lee and Peter R. Shank.

The human immunodeficiency retroviruses are the etiologic agents of the acquired immunodeficiency syndrome (AIDS). The HIV-1 TAT protein is essential for HIV replication. Recently, promising new anti-HIV agents have been identified that inhibit the function of TAT.

The TAT is a potent positive regulator of HIV gene transcription that functions by a novel mechanism involving a direct interaction with nascently transcribed viral mRNA. Our work focuses on elucidating the molecular mechanism of TAT mediated gene activation. In particular, we have analyzed the role of cellular co-factors in TAT function.

We have determined that HIV-1 TAT requires a human-specific cellular co-factor encoded by chromosome 12. We postulate that the TAT protein, cellular co-factor, and nascently transcribed viral mRNA interact to form a ribonucleoprotein complex that is capable of stimulating further viral transcription. A model illustrating the role of TAT in HIV replication will be presented.

7. Concomitant Infection with HIV and HBV—A Retrospective Chart Review

Denis J. Keohane, MD, Michael Spence, MD, Joan Smith, PA-C, Timothy Flanigan, MD

We evaluated 142 HIV-infected patients attending an inner-city hospital-based clinic for concomitant infection with hepatitis B. Hepatitis B antigen or antibody was present in 56, absent in 79 and equivocal in 7. The hepatitis-positive patients were equally divided between the genders. Hepatitis negativity was found in 48 women and 31 men. Injection drug use (IDU) was admitted by 48 of 135 (36%), and 54 individuals were non-drug-using heterosexuals. Hepatitis positivity was more often encountered in IDU patients ($P<0.01$). Individuals acquiring their infection through heterosexual contact were more commonly hepatitis negative ($P<0.005$). When analyzed by gender, hepatitis positivity was more commonly found in women ($P<0.001$). There was no difference in hepatitis positivity between the genders of those acquiring their infection through heterosexual contact.

We conclude that hepatitis B seropositivity is more commonly encountered in IDU women. This may reflect either transmission through injection drug use or increased exposure through sex for drugs. However, hepatitis B seropositivity is uncommonly encountered in individuals acquiring their HIV infection through heterosexual contact without a history of IDU.

8. Splenic Complications of the Acquired Immunodeficiency Syndrome (AIDS)

Robert Dean, MD, (Associate), Edward Feller, MD (Member), Fred Schiffman, MD, FACP, Timothy Flanigan, MD, FACP

Splenomegaly is common in AIDS, occurring in up to 50% of patients. Inapparent, disseminated opportunistic infection or tumor involving the spleen is a frequent autopsy finding. We have seen 2 AIDS patients with the uncommon complications of clinically relevant abscess or tumor involving the spleen. We report these cases to alert physicians to the diverse diagnostic and therapeutic dilemmas of these problems.

Patient 1 is a 34-year-old HIV+ male with a CD4 count=10 cubic mm who was admitted with 2 days of sharp LUQ pain with spiking fevers. CT scan showed a 3 cm low-attenuation area in the spleen consistent with abscess. *Mycobacterium tuberculosis* was cultured from a CT-guided aspirate. He was treated with INH, Rifampin, and Ethambutol with defervescence and resolution of the CT abnormalities. **Patient 2** is also a 34-year-old HIV+ male with a CD4 count=15 cubic mm and a history of Kaposi's sarcoma involving the right lung. He was admitted with splenomegaly developing over 3 weeks, fever, and diffuse abdominal discomfort. CT scan showed hepatomegaly and splenomegaly with multiple, small areas of low attenuation compatible with either tumor or abscess. He continued to spike fevers, developed shock, and died. Autopsy revealed massive splenomegaly (2100g) with multiple focal infarcts and diffuse Kaposi's sarcoma.

In addition to TB or MAI, AIDS patients may develop splenic abscesses due to a variety of bacterial or fungal organisms. The most common route of spread is hematogenous from septic foci, though some abscesses result from infection from a contiguous organ. Of the 18 cases of tuberculous splenic abscess reported in AIDS, most have responded to anti-TB therapy, as in our patient. Splenectomy may be required for cases that fail to defervesce or show persistence of lesions on imaging studies. AIDS patients may also develop widespread splenic involvement with Kaposi's sarcoma or lymphoma that may be difficult to distinguish from abscess or infarct.

9. Sclerosing Cholangitis in the Acquired Immunodeficiency Syndrome (AIDS)

Amy Supnick, MD (Associate) and Edward Feller, MD (Member)

Sclerosing cholangitis is a cholestatic syndrome characterized by inflammation, obliteration, and segmental narrowing of intra- and extrahepatic bile ducts. We have recently evaluated two AIDS patients with severe cholestasis clinically indistinguishable from intrinsic liver pathology who had diffuse sclerosing cholangitis diagnosed by ERCP. We report these cases to alert clinicians to the spectrum of biliary lesions in AIDS and

their management.

Patient 1 is a 28-year-old HIV+ male with a CD4<10 cubic mm who was evaluated for intermittent fever, upper abdominal pain, and jaundice. Alkaline phosphatase=3429 IU, total bilirubin=8.9 mg% with only modest transaminase elevation. Abdominal CT scan was normal. ERCP revealed diffuse stricturing of intrahepatic bile ducts indicative of sclerosing cholangitis. Bile culture was + for *Cryptosporidium*. **Patient 2** is a 34-year-old HIV+ male with a CD4<40 cubic mm who had previously undergone, laparoscopic cholecystectomy for gallstones. He had intermittent fever without abdominal pain and a serum alkaline phosphatase=1025 IU, SGOT=444, and a normal serum bilirubin. CT scan was normal. ERCP revealed segmental stricturing of the intrahepatic bile ducts consistent with sclerosing cholangitis.

In AIDS, upper abdominal pain, fever, or marked serum alkaline phosphatase elevation, occurring alone or in any combination, should prompt consideration of biliary pathology, including diffuse or localized bile duct strictures or ampullary stenosis. AIDS-related opportunistic infections, including CMV, MAI, or as in our patient 1, *Cryptosporidium*, have been documented in biliary ductular tissue or secretions. These lesions may be due to a direct toxic effect of the pathogen or be secondary to an immune-mediated mechanism. Direct cholangiography by ERCP may document the anatomic abnormality, help avoid fruitless evaluation for intrinsic liver disease, diagnose the underlying etiology, and, in selected cases, provide effective endoscopic therapy.

10. Endothelin-I Mediated Vasoconstriction: Specific Blockade by Verapamil.

Nabil S. Andrawis, MD, PhD, Janice Gilligan, RN, and Darrell R. Abernethy, MD.

The capacity of 3 vasodilators that act by distinct mechanisms to reverse endothelin-I (E-I) mediated vasoconstriction was studied in 11 healthy, non-smoking male subjects (age: mean±S.E.M. 26±2 years; weight 74±2 kg) using brachial artery infusion and forearm strain-gauge plethysmography. Isoproterenol (ISO) (c-AHP mediated vasodilation), sodium nitroprusside (NITRO) (c-GMP mediated vasodilation), and verapamil (VER) (L-type calcium channel blocker) were compared for capacity to reverse E-I mediated increase in forearm vascular resistance (FVR). E-I infusion increased FVR 1.9 fold in the control state. ISO infusion decreased FVR with or without concurrent E-I infusion, but at comparable ISO infusion rates E-I increased FVR similar to the control state (ISO 5ng/min; E-I increased FVR 1.85 fold; ISO 12.5ng/min; E-I increased FVR 2.03 fold). Similarly, NITRO infusion decreased FVR with or without concurrent E-I infusion, but at comparable NITRO infusion rates E-I increase in FVR was similar to control (NITRO 0.48mg/

min; E-I increased FVR 1.89 fold; NITRO 0.96mg/min; E-I increased FVR 2.36 fold). In contrast VER infusion decreased FVR with or without E-I infusion and at a VER infusion rate of 19.1mg/min E-I increase in FVR was comparable to control (VER 19.1mg/min; E-I increased FVR 1.36 fold, less than the 1.9 fold increase in the control state; $P<0.05$). ISO and NITRO decrease FVR during concurrent E-I infusion, but do not reverse E-I effect. VER, in contrast, reversed E-I induced vasoconstriction to control FVR, suggesting a specific antagonism of E-I mediated increase in FVR.

11. Hot Epiglottitis in Rhode Island: A Report of Three Cases.

Joseph Spinale, DO (Associate), Michael Mayosmith, MD, Curtis Donskey, MD (Associate), Michi Yukawa, MD (Associate), and Fred Schiffman, MD, FACP.

Acute epiglottitis, a life-threatening illness in both the pediatric and adult populations, is manifested by symptoms of sore throat, hoarseness, stridor, drooling and fever. An inflamed epiglottis can lead to airway compromise and death if not quickly recognized and treated. Infection with *Haemophilus influenzae* type B is the most common etiology. Burns are a rare cause of epiglottitis.

427 adult and pediatric cases of acute epiglottitis were identified from all 12 of Rhode Island's acute care hospitals and the medical examiner's office from 1975 through 1989. The medical records were reviewed for confirmation of the diagnosis by either laryngoscopy or lateral neck x-ray. Cases of epiglottitis associated with an acute thermal injury were identified and are described.

Three cases of thermal injury induced epiglottitis have occurred in Rhode Island over the past 15 years, and all cases have presented within the last 5 years. Thermal injury is the cause of less than 1% of all cases of epiglottitis. All cases occurred in adults during their third or fourth decade of life and were associated with use of illicit drugs, particularly cocaine. None of the patients in this series required acute airway intervention and all improved with conservative regimens including broad spectrum antibiotics, systemic steroids and close monitoring for evidence of airway compromise.

Because of the close proximity of the epiglottis and oropharynx, direct burns of the oropharynx are likely to produce edema of the epiglottis as well as the tissue that is burned directly. Scald injuries to the oropharynx resulting in epiglottitis have been reported in the pediatric population. Thermal epiglottitis in adults is caused by the smoking of illicit drugs, most notably cocaine. It has been postulated that the high temperatures and altered sensorium associated with free-base cocaine causes an extensive necrotizing thermal injury to the hypopharynx and epiglottis. In this series, it was

the accidental inhalation and subsequent swallowing of heated elements of drug paraphernalia that was responsible for the thermal injury.

Thermal epiglottitis causes significant edema of the epiglottis and its associated sequelae. The clinician must keep thermal injury in the differential diagnosis of those patients presenting with signs and symptoms of acute epiglottitis, especially those in high risk groups such as young children exposed to hot liquids and young adults who smoke cocaine. One must consider the possibility of acute epiglottitis and subsequent, airway compromise in those patients presenting with intraoral burns.

12. Relapse of Breast Carcinoma Presenting as a Probable Primary Pituitary Problem

Amy Spomer, MD, Christine Herbert MD (associate), Fred J. Schiffman MD, FACP

Breast cancer is the most common primary tumor which metastasizes to the pituitary gland. This usually occurs in the setting of widely metastatic disease and heavy tumor burden. We describe a 51-year-old woman with breast cancer, metastatic to axillary lymph nodes, treated with surgery and CAF chemotherapy in 1989. In October 1991 imaging studies including bone scan and head CT were undertaken to evaluate the possibility of metastatic disease but failed to reveal abnormalities. In November 1991 she developed fatigue, myalgias, lethargy and weight gain 1 week after receiving a flu shot. Laboratory evaluation including thyroid function tests were undertaken. In December 1991 she noted that she had failed to tan while on vacation in Florida. Physical exam was remarkable for dry skin, peripheral and periorbital edema, and slow recovery phase of deep tendon reflexes with an otherwise normal neurological exam. Laboratory studies revealed low thyroxine and low thyroid stimulating hormone levels. Further investigation revealed low prolactin level, low somatomedin-C and low AM cortisol levels. Repeat CT of the head with sellar cuts revealed a 2 cm in diameter pituitary mass. Magnetic resonance imaging confirmed this and also revealed suprasellar extension. She underwent transsphenoidal hypophysectomy and the mass was found to be consistent with metastatic breast cancer. She recovered fully from her surgery but needed hormone replacement. She soon developed widespread metastatic disease and despite further therapy expired. Pituitary metastases are found in up to one-fifth of patients with metastatic breast cancer but are rare as the initial presentation of recurrent disease. Diabetes insipidus is the most common initial presentation because the posterior pituitary lobe is affected more often than the anterior lobe. Our patient presented with central hypothyroidism as the first manifestation of recurrent disease and demonstrates the need for thorough evaluation of suggested endo-

crine abnormalities in patients with a history of breast cancer.

13. The Hypercoagulability of Polycythemia Vera (PV)—The Clot Thickens

W. Fields, MD, N.J. Freeman, MD, FACP

A 69-year-old man with PV (1982) experienced recurrent thrombosis despite phlebotomy (Hct<50%), hydroxyurea (HU), and anticoagulation. In 1987 he developed right deep vein thrombosis (DVT), was 6 months on coumadin, and began HU for thrombocytosis. In 1990 he had a left DVT and pulmonary emboli (PE) while the Hct was 40% and platelets 473,000/m³. In 1992 he developed right DVT and PE despite coumadin, phlebotomy, and HU with good hematological control. After adding heparin and placing a filter, he required streptokinase for new PE. He later developed 2 new DVTs on adequate coumadin and heparin SQ. PV is a myeloproliferative disorder with excessive marrow production of RBCs, WBCs and platelets. Clinical manifestations including headache, dizziness, visual changes, thrombosis, and bleeding, largely improve with therapy. Thrombosis, often cerebrovascular, is the most common cause of morbidity and mortality and may occur despite good hematologic control. The hypercoagulable state is multifactorial in etiology. Hyperviscosity (Hct>60%) increases the risk of thrombosis by 38 fold vs a Hct of <44%. Erythrocytosis may increase platelet/endothelial contact and thrombosis. Iron deficiency, common in PV, may decrease RBC deformability and increase viscosity. There is no definite correlation between platelet count or function and the incidence of thrombosis in PV, but lowering the count improves symptomatic patients. A few studies demonstrated activation of coagulation in PV. Phlebotomy is indicated to normalize the Hct to <45%. HU should be added to maintain a Hct<50% if the phlebotomy need is high, the age is >70, or with previous thrombosis. P³² and alkylating agents have leukemogenic potential and are discouraged. Interferon and anagrelide improve counts but the role in altering thrombosis is unclear. Treatment of thrombocytosis in asymptomatic patients is controversial; it may be difficult to wait for a first serious thrombotic event. Thrombosis is a major cause of morbidity and mortality in PV. A better understanding of the involved will ultimately improve treatment.

14. An Unusual Case of Acute Renal Failure in a Patient with Multiple Myeloma

Michael Maher, MD, ST Sambandam, MD, Raymond Endreny, MD

Kidney involvement and acute renal failure are sequelae of multiple myeloma that are frequently encountered, and the latter is usually a consequence of hypercalcemia, "dehydration," or "myeloma kidney" ("cast nephropathy"), and less commonly due to "light chain deposition disease" or amyloid-

osis. In our patient, the renal failure was a result of an entirely unexpected process.

A 71-year-old woman was found to have compression fractures of L4 and T3 on an X-ray of her thoracic and lumbo-sacral spine obtained after a work-related injury. The lesions appeared lytic and an MRI exhibited features of infiltration; subsequently a diagnosis of IgA multiple myeloma was confirmed with an IgA level of 3400 mg.%. Her renal function and U/A were normal. Radiation and chemotherapy were initiated. Eight months later the patient had a pathological fracture of her right femur, and at that time her renal function was normal. Two months later, in June 1992, she was admitted with new onset lower extremity swelling associated with weight loss and reduced urine output. Physical examination confirmed bilateral pitting edema, without inguinal masses, suprapubic dullness or CHF. Her creatinine was 4.5 mg.%, calcium 9.8 mg.%, albumin 2.6 gm.%, uric acid 19.3 mg.% with a "spot urine" uric acid:creatinine ratio of 1.5. A renal sonogram revealed bilateral hydronephrosis; a post-void residual was insignificant, and an antegrade study done after insertion of a left-sided percutaneous nephrostomy tube indicated obstruction at the level of the distal ureter. A CT scan demonstrated a large pelvic mass displacing the bladder and rectum, encircling the sigmoid colon and surrounding the iliac vessels at the level of the aortic bifurcation. A CT guided biopsy of the pelvic mass disclosed the presence of a tumor mass consisting of plasma cells. The patient was not treated, expired and an autopsy confirmed the diagnosis of a myelomatous tumor mass with a histologic picture of an anaplastic myeloma that encased both ureters at their approach to the bladder. Histologic exam of the kidney revealed neither "uric acid nephropathy" nor "cast nephropathy."

This case represents a particularly virulent form of multiple myeloma with the distinctly rare presence of obstructive nephropathy due to a plasmacytoma.

15. Acute, Advanced, and Irreversible Renal Failure in a Patient with Waldenstrom's Macroglobulinemia (WMG)

Reginald Gohh, MD, Vishram Reae, MD, Raymond Endreny, MD

Waldenstrom's macroglobulinemia is infrequently associated with advanced renal failure, and it is unusual to develop acute renal failure. This case incorporates both of these features. A 59-year-old black woman with a diagnosis of WMG for over a decade was admitted in November 1991 for therapeutic plasmapheresis when her IgM level was 14.4 gm% and serum viscosity 7.1 (normal up to 1.7). At the time of discharge her creatinine was 1.1 mg.%, and her U/A showed 30 mg.% of protein with a S.G. of 1.010. Less than 2 months later in January 1992 she presented to the emergency room

with symptoms of weakness, and reduced appetite with sporadic nausea and vomiting. Her physical exam found her to be normotensive and euvolemic, and other than diffuse rhonchi due to chronic fibro-cavitary lung disease her exam was benign. A creatinine was 25 mg.%! She was non-oliguric. She was not hypercalcemic, and her renal sonogram did not reveal dilatation of the collecting system; the kidneys were normal in size. Her U/A was unchanged and her serum immunoelectrophoresis was similar to previous ones with an IgM lambda;urine immunoelectrophoresis revealed a Bence Jones protein with lambda light chains. Bone marrow examination was not indicative of multiple myeloma. A kidney biopsy was obtained disclosing the histologic finding of "myeloma" kidney with "cast nephropathy." The patient's kidney function never recovered and she remains on dialysis.

Kidney involvement in WMG is not common, usually not advanced, and rarely acute; the most likely histologic finding in patients with WMG is glomerular capillary occlusion with IgM paraprotein. This patient's clinical diagnosis is highly unusual, and the dual features of acute and advanced renal failure are not expected clinical features of WMG.

16. Two Cases of Upper Extremity Deep Vein Thrombosis

Charles I. Famulare, MD, David S. Pomerantz, MD

Upper extremity deep vein thrombosis (UEDVT) is an uncommon occurrence. Only 11 cases were diagnosed at Roger Williams Medical Center in the 5-year period from 1987 to 1992. The majority (9/11) of these cases had active, serious illnesses (IBD, malignancy, multiple trauma, renal disease, cardiac conduction disease), and each had a record of central venous access for fluid resuscitation, chemotherapy, dialysis, TPN, or pacer placement. The other two cases, with no apparent predisposition, occurred this year and are herein reported.

Case 1: A 40-year-old male complained of 10 days of painful swelling of the right UE (refractory to ASA and warm wraps) with onset 1 week after scuba diving. Ultrasound and venogram confirmed proximal basilic vein thrombosis with collateralization. He was heparinized, converted to coumadin and discharged for 3 months of anticoagulation. Follow-up reveals no residual symptoms or recurrence six months later.

Case 2: A 22-year-old male dancer with HIV risk (but no evidence of infection) developed sudden pain, swelling and bluish discoloration of the left UE. Ultrasound revealed left subclavian thrombosis. Streptokinase and heparin were administered, and he was discharged on coumadin. A hypercoagulable workup was negative (protein C, protein S, anti-thrombin III, lupus anticoagulant, PT, PTT, platelets).

UEDVT represents less than 2% of all cases of DVT. Cases are classified as either spontaneous or trauma-related. Our review confirms that the majority of UEDVT are related to catheterization/instrumentation and that spontaneous UEDVT is rare. We speculate that the 1st case is post-traumatic due to an unusual constriction of the thoracic inlet by the over-the-shoulder tank straps. The second case remains unexplained but the HIV risk and thrombosis merit close observation for the lupus anticoagulant, a known HIV associated hypercoagulable state. Alternatively, dance exercises may have led to the so-called "stress thrombosis" associated with prolonged hyperabduction of the upper extremity.

17. Splenic Hemorrhage Complicating Thrombolysis with t-PA

Christy L. Dibble, DO, and Mark I. Travin, MD

Thrombolytic therapy improves survival of patients presenting with acute MI. The major risk of thrombolysis is hemorrhage. Bleeding has been reported intracranially, systemically, and intraabdominally. We describe a case of splenic hemorrhage following thrombolysis with tissue plasminogen activator (t-PA).

A 58-year-old man admitted with crescendo angina received t-PA for an AWM1 2 days into his hospital course. An early peak CPK of 3623 IU/l and accelerated idioventricular rhythm suggested reperfusion, yet he exhibited infarct extension 5 days later and received a second course of t-PA. The patient developed abdominal pain 36 hours later and had LLQ tenderness to deep palpation. An abdominal CT scan showed a large subcapsular splenic hematoma. Despite anemia and thrombocytopenia, he remained clinically stable and was discharged.

Although bleeding complications have been reported after thrombolysis, we have found only four published reports of splenic hemorrhage. Cerebral bleeding events were consistently noted in the large prospective trials. However, the incidence of nonfatal or clinically minor hemorrhage has been underreported. The manufacturer of thrombolytic agents reveal four unpublished cases of splenic hemorrhage after thrombolysis.

This case is an uncommon presentation of a bleeding complication that would have escaped detection were it not for his persistent complaint of pain. Had the capsule ruptured, the bleeding could have been fatal.

Physicians should be aware of the possibility of splenic hemorrhage following thrombolytic therapy, particularly in patients with left-sided abdominal pain.

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The Practicing Physicians of Rhode Island: A Statistical Profile

Milton W. Hamolsky, MD
Stanley M. Aronson, MD

There are 2747 physicians licensed in the state of Rhode Island. An additional 184 physicians declared themselves to be retired but nevertheless maintained their licenses.

The Rhode Island Board of Medical Licensure and Discipline is responsible for maintaining active records on the demographic characteristics of its licensed physicians. These records include age, school of medicine (or osteopathy) attended and specialty. Registered physicians submit this information when they renew their licenses. The board has now established a computerized database to maintain and review such data.

The data summarized below represent the most recent information gathered by the board. Since not all questions were completely answered in this annual questionnaire, the total number of physicians in each of the demographic categories varies somewhat. At the time of the latest survey, 2747 physicians were licensed in Rhode Island. Another 184 physicians declared themselves retired but nevertheless maintained their licenses.

Except in Tables 2 and 3 (information concerning locations of attended schools of medicine and osteopathy) all statistical summaries reflect combined data from both allopathic and osteopathic physicians. None of the information gathered by questionnaires has been independently verified.

Age

Table 1 summarizes the ages, by decade, of the licensed men and women

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en physicians in the state, both active and retired. Male physicians in active practice, as of January 1993, were, on average, 48.7 years of age; female physicians, on average, were younger (43.1 years.)

The oldest physician in active practice, a former surgeon, is 83 years of age. He had previously served with distinction overseas in various missionary settings both in Africa and the Caribbean region. He is presently involved in the medical care of the chemically addicted and, in addition, conducts bedside teaching for Brown medical students. Few Rhode Island physicians retire before the age of 70; on the other hand, only 47 licensed physicians older than 70 are still in active practice within the state.

About 45 to 50 Rhode Island physicians declare their retirement each year; in addition, about 15 licensed physicians die. The state of Rhode Island therefore needs about 60 to 70 newly arrived physicians to maintain its current complement of practitioners. There are, of course, other forms of attrition (eg, transfers to another state) and the annual replacement num-

bers to maintain a steady state is therefore substantially more than 70. In recent years new physicians have more than replaced the number of those retiring, dying or transferring. A profile of the new physicians entering practice in this state will appear in a future issue of RHODE ISLAND MEDICINE.

Table 1 also provides data to show the increasing participation of women in the practice of medicine within Rhode Island.

Medical & Osteopathic Schools

Table 2 lists the geographic sites, by state or country, of those schools of medicine and osteopathy conferring doctorate degrees upon the licensed physicians of Rhode Island.

The majority of physicians practicing in Rhode Island (allopathic or osteopathic) are graduates of schools located in New England (25.9%) or the middle Atlantic states (29.6%). An additional 24.6% of the practicing physicians received their degrees in medicine from overseas schools.

The great majority of the 127 ac-

Table 1.—Ages of Physicians Licensed in the State of Rhode Island, 1992

Age (yrs)	Active			Retired			% Retired*
	Males	Females*	Total	Males	Females*	Total	
80-89	3	0 (0.0)	3	34	2 (5.6)	36	92.3
70-79	39	5 (11.4)	44	136	11 (7.5)	147	71.7
60-69	389	36 (8.5)	425	1	0 (0.0)	1	0.2
50-59	510	74 (12.7)	584	0	0 (0.0)	0	0.0
40-49	685	168 (19.7)	853	0	0 (0.0)	0	0.0
30-39	576	246 (29.9)	822	0	0 (0.0)	0	0.0
20-29	8	8 (50.0)	16	0	0 (0.0)	0	0.0
Totals	2210	537 (19.6)	2747	171	13 (7.1)	184	6.3

*: percent in parentheses.

+: percent in age category 'retired'. Thus, of 39 members, male and female, in ages 80-89, 36 are retired (ie, 92.3%).

Table 2.—Locations of Schools of Medicine and Osteopathy Attended by RI Licensed Physicians, 1992

<i>Schools of Medicine</i>	
Geographic Site	No. Graduates
New England States	693
Middle Atlantic States	793
Southern States	120
North Central States	180
Midwestern States	86
Southwestern States	31
Northwestern, Pacific States	46
United States, total (MD)	1949 (68.5)*
Canada, total (MD)	54 (1.9)
Mexico	63
Caribbean Islands	55
Central America	1
South America	28
Latin America, total (MD)	147 (5.21)
Austria	5
Belgium	11
Bulgaria	2
Czechoslovakia	3
England	9
France	20
Germany	24
Greece	13
Hungary	6
Ireland	17
Italy	123
Netherlands	5
Rumania	3
Poland	7
Portugal	11
Scotland	7
Spain	4
Sweden	2
Switzerland	10
USSR	8
Yugoslavia	4
Europe, total (MD)	294 (10.3)
Egypt	37
Iran	20
Iraq	2
Israel	5
Jordan	1
Lebanon	10
Sudan	1
Syria	8
Turkey	11
Middle East, total (MD)	95 (3.3)
Africa, sub-Saharan	2
Africa, South	7
Africa, total (MD)	9 (0.3)
China, Taiwan, Hong Kong	22
India	45
Korea	27
Pakistan	11
Philippines	51
Southeast Asia	2
Asia, total (MD)	158 (5.5)
Australia (MD)	1 (<0.1)
Total, licensed MDs	2707
<i>Schools of Osteopathy</i>	
New England States, DO	45
Middle Atlantic States, DO	50
Midwestern States, DO	40
Other, DO	5
Total, licensed DOs	140 (4.9)
Total licensed MDs and DOs	2847

* In parentheses, percent of total.

credited schools of medicine within the United States are represented in the pool of practicing physicians in Rhode Island. Indeed, diplomas from more than 100 different American medical schools may be found on the walls of our local practitioners. The 54 physicians who attended Canadian medical schools list 6 of the 16 Canadian colleges of medicine as their places of undergraduate medical education.

Tufts and Brown Universities have provided 186 and 174 graduates respectively for the practice of medicine in this state. Boston University (110), State University of New York (109), Georgetown (87) and Harvard (69) have also provided medical education for significant numbers of Rhode Island physicians.

Twenty-one of the 25 European nations with medical schools are represented among those practicing in Rhode Island. The largest single group, 123 physicians, were educated in the Italian schools of medicine, particularly those at Bologna, Rome and Padua. (See Commentary in this issue.)

About 3.3% of our practicing physicians received their medical degrees from schools in one or another of the Middle East nations, particularly Egypt (37) and Iran (20). Asian universities provided medical education for 158 Rhode Island physicians, particularly those schools situated in India and the Philippines.

Table 3 lists those 24 schools of medicine and one school of osteopathy attended by 25 or more of the licensed physicians of Rhode Island. Beyond New England, only schools in New York, Pennsylvania, New Jersey, the District of

Table 4.—Specialties (Self-Declared) Practiced by RI Licensed Physicians, 1993 (Percentages)

Specialty	US, 1976*	US, 1986*	RI, 1992**
Allergy, Immunology	0.5	0.6	0.6
Anesthesiology	3.8	4.6	5.0
Dermatology	1.4	1.3	1.8
Emergency Medicine	0.8	2.4	3.1
Family Practice	3.8	8.4	7.5
General Practice	12.1	5.0	4.4
General Surgery	9.5	7.6	6.0
Internal Medicine	19.8	22.9	22.6
Neurology	1.3	1.6	2.0
Neurosurgery	0.9	0.8	1.2
Obstet/Gynecology	6.4	6.2	6.8
Ophthalmology	3.3	3.0	2.8
Orthopedic Surgery	3.4	3.5	4.3
Otolaryngology	1.7	1.5	1.4
Pediatrics	6.8	7.5	8.9
Psychiatry	7.8	7.2	8.7
Physical Medicine	0.5	0.7	0.9
Plastic Surgery	0.7	0.8	1.0
Pathology	3.5	3.1	3.9
Radiology	4.5	5.2	4.1
Thoracic Surgery	0.6	0.4	0.3
Urology	2.0	1.8	1.6
Other	4.9	3.9	1.1

* Nationwide data derived from American Medical Association.

** Data from R.I. Board of Medical Licensure & Discipline

Columbia, Ohio and Missouri are listed. Two overseas schools have each trained at least 25 local physicians: Guadalajara in Mexico and Bologna in Italy.

Specialties Practiced by RI Licensed Physicians

Table 4 summarizes the self-declared primary specialties of the Rhode Island practitioners of medicine. Table 5 places these specialties into broader categories (ie, surgical, non-surgical, institutional). There are no notable departures from data collected nationally. The institutional specialties, incidentally, are defined as those specialties which are typically based in institutions (eg, pathology, radiology, physical medicine.)

Comment

It is the intent of the Rhode Island

Table 3.—Schools of Medicine and Osteopathy Attended by 25 or More of the Licensed Physicians of Rhode Island, 1992

New England

Tufts
Brown
Boston
Harvard
New England
(osteopathy)
Yale
Massachusetts
Vermont

Middle Atlantic States

State Univ New York
Georgetown
New York Medical
New York Univ
Columbia
Cornell
Albany
Jefferson
Rochester
Pennsylvania
George Washington
New Jersey
Hahnemann

Midwestern States

Case Western Reserve
St. Louis

Latin America

Guadalajara

Europe

Bologna

Board of Medical Licensure and Discipline to provide an annual statistical profile of the practicing physicians of this state. As the questions in the annual questionnaire increase in number, the amount and diversity of summary information will necessarily increase.

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Table 5.—Major Categories of Specialties (Self-Declared) Practiced by Licensed Physicians of Rhode Island, 1993

Specialty	US, 1976*	US, 1986*	RI, 1992**
Non-Surgical	53.5%	54.6%	56.7%
Surgical	32.5	30.8	31.9
Institutional	8.5	9.0	8.9

*: Data derived from American Medical Association

** : Data from R.I. Board of Medical Licensure & Discipline draft



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The Unifying Principles of Family Medicine: A Historical Perspective

Vincent R. Hunt, MD

"The principles of family medicine are universal, whereas family practice will vary from place to place according to local needs." Jack H. Medalie

Since obtaining specialty designation in 1969, family medicine has received recognition and acceptance on the national and international level. Nevertheless, progress has been associated with formidable challenges, especially from the academic community. This article will delineate the nature of these challenges within a historical perspective, describe the principles underlying the family medicine movement and consider the quality of care provided by family physicians.

Decline of General Practice

Sixty years ago, more than 80% of practicing physicians in the United States were general practitioners. During the next 40 years, this number fell precipitously and, by 1970, only one out of five physicians in private practice was a general practitioner;¹ 45% were over 55 years and their median age had increased to 50.^{2,3} Furthermore, these aging physicians were not likely to be replaced because fewer than 8% of medical school graduates were entering general practice.⁴ There was little support for this discipline in medical schools where professors frequently referred to "the local MD" in derogatory terms. General practition-

ers often worked longer and had more irregular hours than their specialty counterparts. Their privileges were curtailed in hospitals and by 1970 the Joint Commission on Accreditation of Hospitals (JCAH) had limited hospital departments of general practice solely to organizational functions.⁵ Thus, along with all their other problems, it appeared that general practitioners would soon be excluded from effective involvement in the care of hospitalized patients.

This trend began during World War II when the United States mobilized medical personnel along specialty lines. Those going into specialty training often were deferred from serving in the armed forces. Better assignments and higher ranks went to specialists rather than general practitioners. Following the war, medical knowledge expanded rapidly. There were remarkable technological advances and research was subsidized heavily through federal and private agencies.⁶⁻⁸ Emphasis on in-depth investigation enhanced by funding incentives led naturally to subspecialization within the medical schools. Students emulated their mentors, while the generalist clinician was hard to find in the academic setting and often was not valued as a role model or teacher.⁸ Indeed, many university educators, who were removed from primary care, believed it was not possible to train physicians to manage such a wide variety of disorders, most of which appeared to be so complex within the tertiary care setting.

These impressive scientific advances, however, overshadowed the fact that care was becoming fragmented, depersonalized and costly. Patients had difficulty finding the right physician for their particular disorder. Often it was necessary for them to consult several physicians if their problems in-

... the unspoken covenant with the patient is that his or her medical problems, whatever their nature, will be addressed in an ongoing, coordinated and comprehensive manner.

volved more than one organ system or specialty discipline. Gradually, many communities were depleted of general practitioners. Rural areas and poorer sections of the cities were affected most because specialists congregated in the more affluent metropolitan locations. Neither student nor teacher received adequate exposure to common illnesses, especially in the ambulatory setting, and diseases were seldom viewed in relation to their early natural history or from the perspective of prevention. Often, familial influences and psychosocial variables were overlooked. Furthermore, because patients were seen outside the context of their home environment, it was difficult to appreciate how socioeconomic circumstances or cultural background affected their health.

These concerns are remarkably sim-

ABBREVIATIONS USED

AAGP: American Academy of General Practice
AAMC: Association of American Medical Colleges
ACGME: Accreditation Council for Graduate Medical Education
AMA: American Medical Association
CHD: Congestive heart disease
COGME: Council on Graduate Medical Education
COPD: Chronic obstructive pulmonary disease
ENT: Ear, nose, and throat
JCAH: Joint Commission on Accreditation of Hospitals
LCME: Liaison Committee on Medical Education
MUSE: Minimum Uniform Standards of Education for General Practice
URI: Upper respiratory infection
UTI: Urinary tract infection

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ilar to those being articulated currently. Nevertheless, the forces propelling medicine toward specialization and reductionism are potent, and this trend continues to accelerate. Consequently, besides 26 approved specialties, there are now 56 accredited subspecialty residency programs, over 60% of which have come into existence in the past 6 years. Because of this alarming proliferation, the Accreditation Council for Graduate Medical Education (ACGME) declared a moratorium on certification of new programs until June 1993.⁹

A Counter-trend Leading to Certification

Despite the preeminence of subspecialization, the ideal of a well-trained generalist capable of caring for the majority of common illnesses persisted. In 1945, the American Medical Association formed a section on general practice. Two years later, efforts by officers of this section and leaders in several state general practice organizations culminated in the formation of a national organization, the American Academy of General Practice (AAGP).^{*} Although this new organization was initiated as a response by beleaguered practitioners to economic and political forces threatening their survival, a sense of altruism and the importance of quality evolved as well. For instance, the AAGP was the first medical organization in the United States to require continuing education to retain membership.

During the late '40s and '50s there were numerous attempts to combat the dwindling number of general practitioners¹⁰ (Table 1). The AMA appointed a series of committees to study the causes of this decline and propose solutions, the echoes of which are still heard in the '90s. For instance, in 1947, AMA President Harrison Shoulters, MD, appointed the Special Committee to Study Conditions of General Practice, stating that "the immediate and most urgent needs are concerned with increasing the availability of the services of general practitioners." This committee's report to the AMA House of Delegates 1 year later emphasized

^{*}The name was changed to the American Academy of Family Physicians (AAFP) in 1971.

Table 1.—Chronology of Key Events in Evolution of Family Medicine Specialty

Date	Event
1940s, '50s, '60s	Numerous resolutions and recommendations pertaining to post graduate training and specialty certification in the AMA House of Delegates and AAGP Congress Event of Delegates
1945	AMA forms section on General Practice
1947	Formation of American Academy of General Practice (AAGP)
1947	Special committee to study conditions of General Practice (AMA)
1949	Committee on General Practice (AMA)
1957	Committee on Preparation for General Practice (AMA)
1957	Committee on Minimum Uniform Standards of Education for General Practice (AAGP)
1950s & '60s	A variety of pilot training programs
1965	Planning for <i>Medical Progress Through Education</i> (AAMC) "Coggeshall Report"
1965	AAGP Board authorizes planning for a certifying mechanism
1966	<i>Ferment in Medicine</i> , Richard Magraw
1966	Ad Hoc Committee on Requirements for Certification (AAGP-AMA) produces the Core Content of Family Medicine
1966	<i>Health is a Community Affair</i> (American Public Health Association and the National Health Council) "Folsom Report"
1966	Citizens Commission on Graduate Medical Education (AMA) "Millis Report"
1966	Ad Hoc Committee on Education (AMA) "Willard Report"
1969	Approval of Family Practice as the 20th American Specialty

the importance of at least 2 years of post-graduate training for general practitioners, stressed meaningful representation and privileges within every general hospital and urged that post-graduate education for general practitioners be made more widely available. These recommendations paved the way for a variety of resolutions and recommendations within the AMA during the subsequent decade. In 1949, the House of Delegates passed one such resolution urging that 2-year rotating internships be developed rapidly and that they be designed especially for those wishing to be general practitioners. In 1950, the Committee on General Practice reported to the AMA House of Delegates that too many specialists and too few general practitioners were being trained. Committee members addressed the charge of "how to stimulate the formation of a department of general practice in each medical school" and concluded in 1956

that general practice had to be defined further to determine the "best indoctrination for the individual who plans to enter the field of general practice." This led to a new Committee on Preparation for General Practice. This committee spoke of the "family physician" and defined family practice as "that aspect of medical care performed by the doctor of medicine who assumes comprehensive and continuing responsibility for the patient and his family, regardless of age." The AMA's Council on Medical Education and Hospitals approved their report in 1959. It stressed that there should be a unified, coordinated 2-year graduate education program for family practitioners to include following patients in the ambulatory setting over long periods of time. This approach was intended to simulate the close interpersonal relationship that develops during the ongoing association of physician and patient.

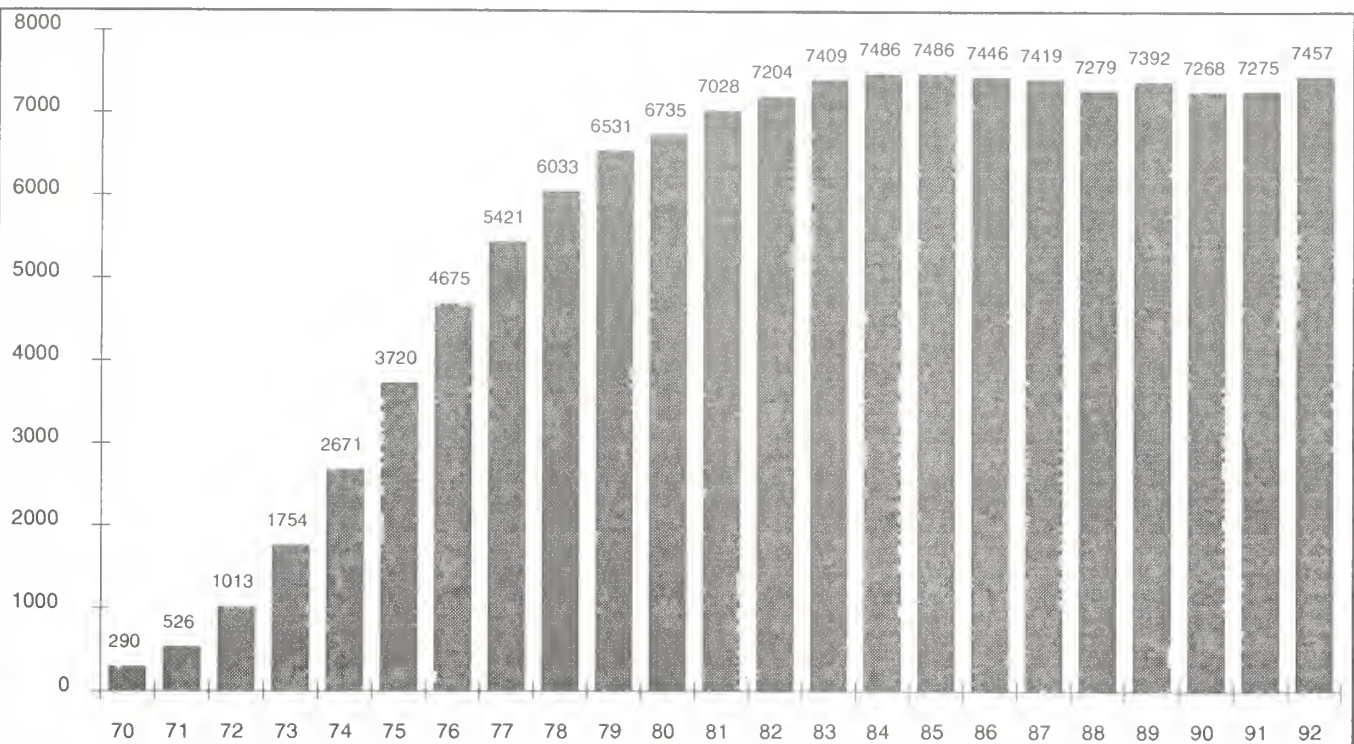


Fig 1.—Number of Residents in Family Practice Programs. Source: American Academy of Family Physicians Residency Census, July 1992.

Concomitant with the AMA's activities, the Board of Directors of the AAGP formed a Committee on Minimum Uniform Standards of Education for General Practice (MUSE). This committee proposed creation of a 2-year graduate training program leading to certification by a Board of General Medicine.¹¹ The AAGP Board of Directors approved these recommendations in 1958. However, the Congress of Delegates did not. Instead, they advised further study and liaison with the AMA Section on General Practice and the Advisory Board for Medical Specialties.

Although proposed in the past by a few, more medical leaders were becoming convinced in the early 1960s that specialty status for the generalist along with certification examinations and well-planned residencies were the only way to attract medical students and assure quality in their training. These advocates met strong opposition from many specialties. Vigorous debates centered on whether obstetrics and surgery should be included as integral components of family practice. Others were concerned about increased competition from the proposed new specialty. Even general practitioners opposed these ideas. Some did not see the value of extra training.

Many older practitioners believed these developments would be unfair to them, and that their reputations might suffer in comparison with the younger physicians who would now be certified as specialists.

Events in 1962 symbolized these contradictory forces. During this year, the AAGP Congress of Delegates rejected the idea of a Board of General Practice while at the same time the Academy's journal, *GP*, published an article titled "An American Board of General Practice for Family Physicians," that was prepared by the executive committees of the AAGP and the AMA Section on General Practice.¹² This article presented a series of arguments for and against a board to provide a balanced perspective. During the following year, the president of the AAGP spoke against board certification while the board of directors adopted a recommendation favoring a certifying board. In 1963, however, the AAGP president informed the Congress of Delegates that the board of directors were now united with them in opposition to a board of general or family practice.

Meanwhile, as resolutions were being debated and committees formed, a variety of pilot training programs were initiated. The options for medi-

cal students included 2-year training programs designed for general practice, which were subject to review by the Residency Review Committee for General Practice, 2-year programs, not subject to this review, some of which required surgery and obstetrics and some which did not; 1- and 2-year rotating internships and 2-year programs for physicians who had completed a 1-year rotating internship. None of these routes to general practice succeeded and few students were attracted.^{10,13} Most programs failed to provide high quality educational experiences. They were poorly coordinated and lacked thorough planning while service often took priority over teaching. General practice continued its precipitous decline. In view of the past failures, however, the arguments and efforts of the advocates for board certification gained ascendancy and in 1965 the chairman of the AAGP board, Herman Drill, MD, argued persuasively for well defined residency programs and certification. The board of directors now reversed themselves and authorized planning for a certifying mechanism. Still another committee was formed to determine requirements for certification. This committee, composed of members from the AAGP and the AMA Section on General Prac-

Table 2.—Health Care Problems Pertaining to Family Medicine Addressed by Numerous Committees over the Past Five Decades

1. Fragmentation
2. Depersonalization
3. Escalating costs associated with:
 - Over reliance on technology
 - Lack of coordination
 - Difficulty knowing which physician to contact
 - Necessity of consulting several physicians for common problems
 - Delivery of primary care by specialists who are not trained or psychologically oriented for this task
4. Maldistribution and lack of access, especially inner cities and rural areas.
5. Barriers to hospital privileges for general practitioners.
6. Lack of supportive environment for educating generalists in medical schools and residencies:
 - Imbalance between medical school priorities and needs of society.
 - Overemphasis on reductionism, diseases in advanced stages and tertiary hospital setting.
 - Lack of family physician role models, training in ambulatory care and student exposure to common illnesses including preventive medicine and health maintenance.
 - Curriculum fragmented by competing interests of each specialty department
 - Disproportionate funding for biomedical research and concomitant subspecialization
 - Lack of academic recognition and research funding for family physicians
 - Lack of specialty certifying mechanism for family medicine.

tice, produced *The Core Content of Family Medicine*, which was adopted by the AAGP Congress in 1966.¹⁴ A distinguishing feature of this formative document was its emphasis on the importance of the behavioral sciences as integral to the training of family physicians.

In the mid-'60s a variety of other forces began to coalesce, embodied in a prescient book by Richard Magraw, MD, titled *Ferment in Medicine*.¹⁵ He analyzed the changing nature of medical education, practice, organization and financing resulting from the rapid technological advances and expansion of biological knowledge. He described how the tertiary hospital-oriented view of disease altered the perspective of medical education and warned of the deemphasis on teaching engendered by overwhelming funding for research as opposed to education. He showed how these changes contributed to a mechanistic concept of illness, fragmentation of care with subsequent breakdown in the personal doctor-patient relationship, and disruption of the previously understood contract between physicians and society, which

included care for the underserved. Although he did not specifically advocate general practice, Magraw laid the intellectual groundwork for this discipline by stressing the inadequacy of isolated specialty care and the need for synthesis, coordination and teamwork.

In 1965, the Association of American Medical Colleges (AAMC) published the results of a study by a special planning committee chaired by Lowell Coggeshall, MD.¹⁶ This report noted the dramatic rise in specialization and predicted that this trend would increase over the forthcoming years. At the same time, the authors pointed out that "some means will need to be found for providing family physicians—physicians prepared to accept overall responsibility for their patients care over extended periods of time." They emphasized the need for more and better prepared physicians who could work with other colleagues and health care providers as a team. The authors did not spell out the specific education for these doctors but did stress that medical educators must accept responsibility for training physicians to meet the needs of the "na-

tion, state and community for health care and personnel." They stated "there is, perhaps, no implication of emerging trends that has more profound significance for the field of medical education today than the need to give increasing attention to the growing health requirements of the nation." Also, they noted that, among physicians, there was a growing sense of responsibility for the health needs of society and a declining emphasis on "entrepreneurial philosophy." From the vantage point of 28 years this committee had considerable influence on the reorganization and direction of the AAMC, yet its exhortations to medical centers generally have not been followed and, for the most part, its expectations of physician behavior were not fulfilled.

In the following year, a commission of the American Public Health Association and the National Health Council chaired by Marion Folsom, MBA, LLD, published a report titled *Health Is a Community Affair*.¹⁷ This report was based on the findings and recommendations of six task forces composed of 10 to 15 members and 21 community self-studies that analyzed needs and developed suggestions for comprehensive health services. Furthermore, these members enlisted responses from 1000 community leaders throughout the country. They presented their 14 major positions to President Johnson on April 22, 1966, pointing out that every community needed "comprehensive personal health services of high quality" and that "every individual should have a personal physician who is a central point for integration and continuity of all medical and medically related services to his patient." They believed that this physician should have a staff appointment in accredited hospitals with privileges according to his or her capabilities and that continuing medical education programs should be made available to these "personal physicians." They advised that, to attract medical graduates to this type of career, the importance of this role must be recognized, and this position should be "accorded status, professional satisfaction and income comparable to that of other physicians." The authors recognized the immensity of this task and acknowledged that significant financing would

Table 3.—Basic Principles of Family Medicine

1. Provision of continuity of care focused on a personal relationship with patients over time
2. Responsibility for comprehensive care of patients regardless of:
 - Age or sex
 - Differentiation of illness
 - Specific organ or system dysfunction
 - Disease entity or presenting complaint
3. Management of the majority of patients' health care problems emphasizing:
 - Expertise in frequently occurring diseases
 - Accessibility, prevention, early detection and health maintenance
 - Coordination of consultations, referrals and resources within the community and hospitals
 - Cost effectiveness
 - Care within the context of patient's family unit, environment, culture and values
 - Integration of the biological, clinical and behavioral sciences
 - Systematic approach with increasing orientation for care of populations at risk and the underserved
 - Decision-making consistent with the prevalence of disease in the population being treated
4. Functional content derives from a selective synthesis of other specialties plus contributions from research and scholarly work specific to family medicine and primary care

be necessary to support teachers and trainees comparing it in "magnitude to that which expanded medical research in the past 2 decades." This report had considerable impact on the development of neighborhood health centers and added further documentation of society's need for personal physicians; yet, again, it did not seem to have much effect on medical educators.

Perhaps the two most influential studies in the mid-'60s were those commissioned by the American Medical Association. In August 1966, the Citizens Commission on Graduate Medical Education chaired by John S. Millis, PhD, published its recommendations.¹⁸ This commission observed that the rapid rise in specialization was associated with fragmentation in medical education and imbalance in delivery of health care. Their report helped establish a conceptual base for family medicine by emphasizing the importance of a "primary physician" who would provide continuous and comprehensive care for all. The committee also insisted that training programs be affiliated with academic centers to assure quality education comparable to that of other specialties.

Another report with far-reaching consequences was published 1 month later. It was prepared by the AMA Ad Hoc Committee on Education under

the chairmanship of William Willard, MD.¹⁹ Dr Willard's committee defined the family physician more succinctly, provided a structure for training such physicians over a 3- to 4-year period, emphasized the importance of a model ambulatory unit simulating a family-oriented practice and stressed the necessity for board certification with periodic recertification.

Both studies focused on the need for personal physicians who would:

- view patients as unique individuals;
- identify problems within the framework of their family, society and culture;
- manage the majority of these problems;
- seek appropriate consultation when indicated; and
- coordinate their overall health care throughout their lives.

This physician was eventually termed a "family physician" although many other titles were considered by a variety of committees over the years, such as: general practitioner, personal physician, first contact physician, comprehensive care physician, and primary physician.

The "Millis" and "Willard" reports gave considerable impetus to the family medicine movement. Furthermore, during the mid-'60s rising social consciousness in the United States rein-

forced the concepts articulated in those two documents. The conclusions of these committees were published in newspapers and magazines. Public awareness increased, and citizens became concerned. Legislators and government officials responded with interest. Specialty status was now considered seriously by the appropriate certifying organizations and on February 8, 1969, 3 years after publication of these two reports, the Council on Medical Education of the American Medical Association and the American Board of Medical Specialties approved the new specialty of family practice.

Fifteen residencies were approved in 1969, and the first board examinations were given in 1970. The family medicine movement developed rapidly over the next decade. By 1980, there were 382 residencies²⁰ and 6735 residents in training.²¹ About 15% of US medical school graduates, many of whom were highly ranked by their respective schools, chose family practice residencies.^{22,23} And more than 85% of all medical schools had departments, divisions or sections of family practice.²⁴ During the '80s, however, this growth subsided and student interest diminished (Figure 1). Even though 40 new medical schools have evolved since the early '60s with more than doubling of enrollment and an increase of the physician population ratio from 140 to more than 240 per 100,000,²⁵ the number of family physicians continues to decline. Only 10.3% of US medical school graduates became first year residents in family practice in 1991.²⁶ As indicated in Figure 1, this number increased slightly in 1992, but the number of graduates is not keeping up with the attrition of family physicians. As of 1990, only 11.4% of physicians in the United States were registered by the AMA as either family physicians or general practitioners.²⁷ The problem is even more serious for general internal medicine and pediatrics. Their number of trainees is diminishing, and a large percentage of physicians who are registered as residents in these disciplines eventually pursue subspecialty training. Moreover, because of the lack of generalists, many specialists and subspecialists assume comprehensive care for their patients, a task for which they

Table 4.—Frequency Distribution of Diagnoses in the Family Care Center, Department of Family Medicine, Brown University/Memorial Hospital of Rhode Island July 1, 1989-June 30, 1990

Diagnoses	# of Diagnoses (Total = 34,517)	% of All Diagnoses	Cumulative (%)
1. Well Child Care	2727	7.90%	7.90%
2. Prenatal	2347	6.80%	14.70%
3. Family Planning	2174	6.30%	21.00%
4. Physical Exam	1861	5.39%	26.39%
5. Hypertension	954	2.76%	29.15%
6. Med/Surg/Lab/Nurse	713	2.07%	31.22%
7. Otitis Media	658	1.91%	33.13%
8. Diabetes	617	1.79%	34.91%
9. Tobacco Abuse	574	1.66%	36.58%
10. Postnatal Care	508	1.47%	38.05%
11. Viral Syndrome	478	1.38%	39.43%
12. Advice/Education	413	1.20%	40.63%
13. Diagnosing Pregnancy	410	1.19%	41.82%
14. Obesity	373	1.08%	42.90%
15. U.R.I.	371	1.07%	43.97%
16. Depression	338	0.98%	44.95%
17. Lipid Disorder	312	0.90%	45.86%
18. Abdominal Pain	297	0.86%	46.72%
19. Back Pain	269	0.78%	47.50%
20. Vaginitis	220	0.64%	48.13%
21. Laceration	219	0.63%	48.77%
22. Asthma	214	0.62%	49.39%
23. Acute Bronchitis	212	0.61%	50.00%
24. Anxiety	211	0.61%	50.61%
25. Angina/CHD/Ischemia	204	0.59%	51.20%
26. COPD/Emphysema	200	0.58%	51.78%
27. Cystitis, UTI	200	0.58%	52.36%
28. Other Female Problems	191	0.55%	52.92%
29. Family Planning Guidance	187	0.54%	53.46%
30. Heart Failure	157	0.45%	53.91%
31. Alcohol Abuse	152	0.44%	54.35%
32. Boil/Cellulitis/Abscess	132	0.38%	54.74%

are neither specifically trained nor psychologically oriented.

Recent Developments

Again, we have seen a flurry of reactions to the decline of generalists, many of which are likely to vitalize the family medicine movement. In 1988, the Macy Foundation held a national seminar on medical education.²⁸ This conference brought together about 30 experts to assess the clinical education of medical students concerning the needs of society and to recommend appropriate changes. The majority of these committee members recommended centralizing control of medical curriculum within the dean's office to counteract the lack of a consistent direction engendered by the competing interests of each specialty department. Also, they advised that med-

ical schools be responsible for residencies, more training be provided in ambulatory care settings, and funds be shifted from the "inpatient to the outpatient programs to permit such education to occur."

In 1986, Congress authorized the Council on Graduate Medical Education (COGME) to provide an ongoing assessment of physician personnel trends and to recommend efforts to address identified needs. In its third report to Congress on October 27, 1992,²⁹ this council predicted that, in spite of the large increase in the number of physicians trained nationally, the alarming trend toward specialization would lead to more costly primary care services when provided by subspecialists and further aggravate the lack of access to medical care for those in the inner cities and rural areas. This report recommended that gradu-

ate medical education funding for residency positions be predicated on state and regional personnel needs and national goals. This approach to allocation, based on openly determined province-wide needs, has worked successfully in Canada. COGME further recommended that 50% of medical students should pursue residencies in the generalist disciplines of family practice, general internal medicine and general pediatrics.

In September 1992, the AMA published the report of the Medical Schools Section Primary Care Task Force.³⁰ This committee provided a variety of recommendations to increase the number of primary care physicians in our country and to improve the care of underserved populations. During this month, the ACGME passed a policy statement expressing readiness "to participate with a national effort designed to assure that an appropriate balance is restored to the mix of generalist and non-generalist physicians." Recently, the Pew Health Professions Commission defined competencies for generalists and outlined strategies to increase their numbers to at least 50% of residency positions.³¹ Also, the Robert Wood Johnson Foundation has undertaken an ambitious initiative to stimulate generalist training in the medical schools.³²

In association with the report of its *Task Force on the Generalist Physician*, the AAMC released a policy position on October 8, 1992,³³ described as a major new undertaking, which "advocates as an overall national goal that a majority of graduating medical students be committed to generalist careers (family medicine, general internal medicine, or general pediatrics) and that appropriate efforts be made by all schools so that this goal can be reached within the shortest possible time." This new AAMC policy, which reverses decades of opposition by many members of this organization, asks all medical schools to establish administrative units for the generalist specialties to assure adequate funding, support and leadership for training generalist physicians. They recommend that generalists be given appropriate academic, administrative, and leadership roles; that all medical students have meaningful curricular experiences in the generalist special-

Table 5.—Diseases of the Ear.

Rank Order Frequency	Diagnoses	Frequency	Percent
8	Otitis media, acute	665	73%
91	Otitis externa	61	7%
96	Cerumen, impacted	54	6%
118	Other ear problem	53	6%
99	Hearing problem	49	5%
130	Serous otitis media	34	3%
Total # of diagnoses 7/1/90-6/30/91 = 34,532			
ENT diagnoses represent 2.65% of this total			

ties; and that medical schools adjust their mission criteria to increase the matriculation of applicants likely to enter a generalist career. To enhance these policies, the AAMC has established an office charged with coordinating implementation of these strategies.

Another significant development has occurred in the wording of the Liaison Committee on Medical Education (LCME) document, which governs medical school accreditation.³⁴ After 7 years of debates, the latest version mentions family medicine specifically as one of the six major disciplines in which students should gain clinical experience, thus providing curricular parity with the traditional medical school specialties of internal medicine, pediatrics, obstetrics/gynecology, surgery and psychiatry. Although still not ratified by the LCME's parent organizations, the Council on Medical Education of the AMA and the executive committee of the AAMC, approval is expected. This action could represent a breakthrough in academic acceptance for family medicine.

Worldwide Movement

As might be expected, these developments are not limited to the United States. Similar forces are operative in a variety of geographical settings and, thus, many countries are turning to family medicine as the foundation for a more rational, coordinated and cost effective health care system. For instance, the World Health Organization has stressed the need for more family physicians and has emphasized the importance of postgraduate education programs designed specifically

for physicians entering family practice.³⁵ This discipline is well established in Australia, New Zealand and Canada, making up half of these country's doctors and in Great Britain where 70% of physicians are general practitioners. Programs are operative throughout Mexico, Israel, Latin America, Europe and Korea. Many Asian-Pacific and Middle Eastern countries have initiated family practice programs as have India, Pakistan, Egypt, China and Russia. Over 50 countries now have established programs in family medicine or general practice. Most of them face problems of even greater magnitude than those we encounter in the United States. Nevertheless, the ideals persist as articulated in the *Alma Ata Proclamation of Health for All by the Year 2000*³⁶ and more recently, in the Edinburgh Declaration,³⁷ which represents a global effort of participants from 67 countries to assure that the training of physicians is congruent with the health needs of nations and their communities.

Underlying Principles of Family Medicine

Upon reviewing this long history and all the struggles that impeded family medicine's development, one wonders why this profession has persisted in spite of the formidable forces arrayed against it. Perhaps its resilience relates to the problems in medical education and health care that have occupied numerous committees over the past half century (Table 2). Solutions to these problems have not been addressed by the majority of our medical leadership. Thus, it is no accident that the specialty of family medicine arose

more from pressures from the public than from a supportive academic community. Deliberations by those involved in this regenerative process served to elucidate the principles underlying family medicine (Table 3). Although there have been many attempts to define and describe this specialty, most of its characteristics are encapsulated by a few fundamental concepts such as continuity of care, a comprehensive approach and acceptance of undifferentiated patients regardless of age, sex, disease entity or organ-specific dysfunction.

Continuity of Care

An ongoing personal relationship is a characteristic that is important in most fields of medicine, but it is the essence of the family physician's work.³⁸ Continuity extends from preconception care to helping patients die with dignity and equanimity. It includes visits to the home when necessary as well as the nursing home and hospital. It is impossible to provide 24-hour continuity, but nevertheless family physicians strive to be available when needed. When they are absent, however, continuity is provided through colleagues and an informative record system using the problem-oriented approach, flow sheets, problem lists and appropriate audits.

Continuity facilitates preventive medicine and health maintenance. It is much easier and usually more cost effective when these activities are carried out in an organized manner over time with successive office visits. Furthermore, this relationship serves as an additional diagnostic aid, allowing ongoing observation to clarify the nature of the patient's problem. If it is not an immediate threat to life, close follow-up provides the astute physician opportunity to sort out the probabilities while watching the patient closely for an atypical course suggesting need for more active intervention. In this way, many problems are clarified or resolve spontaneously, costs are reduced and iatrogenic risks diminished.

Comprehensive Approach

As medicine becomes more specialized and technologically oriented, there is an increased need for a gener-

alist to provide comprehensive care to the whole patient. Frequently, it is necessary to consider psychosocial, financial and cultural influences on the patient's health and the impact of the family and community. Preventive medicine is an essential component of comprehensiveness, as is coordination of care for the patient who must see other specialists or health care providers. Thus, the family physician is expected to review issues revolving around sexuality with the teenager coming for help with acne, pneumovax and tetanus immunization in elderly patients presenting with arthritis, and solar protection, stress management and heart healthy practices for the middle aged executive with bronchitis. A comprehensive approach is especially important for patients with terminal illness who are often faced with a bewildering array of specialists. In such situations, patients need a generalist to provide care for the majority of their problems and to coordinate referrals and consultations in a compassionate, competent manner consistent with their beliefs and values.

To assure a comprehensive approach, physicians must possess a mature awareness of their limitations and the self-confidence to seek help when necessary. This is one reason why educational activities in family medicine have been so closely associated with psychiatry and the behavioral disciplines. This training helps family physicians integrate psychosocial considerations and counseling into their care. Moreover, the quality of their clinical decisions is enhanced through greater insight into themselves and their reactions to their patients.

Dealing with Undifferentiated Problems

The family physician cares for patients who have not been preselected or screened. Each patient represents a unique challenge and can present in various stages of illness, ranging from symptoms of a cold to emergencies such as myocardial infarction and meningitis or more rare entities such as neuroblastoma or vertebral osteomyelitis.³⁹

Undue need for closure can result in costly tests, dangerous invasive pro-

cedures and anxious patients. To avoid overlooking significant clinical findings, the family physician must retain a critical approach and define problems according to available knowledge, avoiding the extremes of over and under-diagnosing. This is a challenge to all physicians. However, because of the diversity of presenting symptoms and the potential for serious illness with each encounter, family physicians have to be highly attuned to recognizing deviations from the natural course of the disease under consideration and alert to cues suggesting unusual diseases, complications or failure to respond to the usual treatments.

There is a natural desire among physicians to limit the types of patients whom they treat. This is done in a variety of ways such as accepting only those in a certain age range or with specific diseases. This is understandable, because it allows physicians to feel that they have mastery over a defined set of problems. Family physicians, however, have to be prepared to deal with a variety of concerns; their patient contacts are based more on a personal relationship than a specific disease entity. Patients can turn to these generalist physicians, expecting a therapeutic interaction regardless of their age, sex, disease or organ dysfunction. Even if this results in a referral or consultation, the unspoken covenant with the patient is that his or her medical problems, whatever their nature, will be addressed in an ongoing, coordinated and comprehensive manner.

The undifferentiated nature of family medicine can be unsettling to those who desire a high degree of certainty in their actions. Perhaps this desire is even more prevalent among academic physicians who may have a greater need for certainty and recognition of their expertise. If so, they are more likely to reject the family medicine approach and question its quality. This makes it even more difficult for family medicine to establish a secure presence in the modern academic medical centers.

The Importance of Quality

One test of a scientific approach is that a hypothesis responds to and ex-

plains a full range of variables affecting the problem at hand. From this perspective, family medicine is challenged to be the most scientific of all the medical specialties. The family physician is expected to develop a working hypothesis that takes into account the nature of the illness and all its manifestations, the unique personality of the patient and the context of the patient's relationship to his or her family, community and life circumstances—and to do this in an efficient, cost effective manner within the confines of an average office visit. Naturally one wonders whether this can be done according to rigorous scientific standards.

Fortunately, competence is possible because generalist physicians acquire expertise in the frequently occurring problems of their patients. For instance, many studies have shown that about 25 problems make up half of medical diagnoses in family medicine.

Studies at our institution confirm this as reflected in Table 4. Furthermore, by breaking down these encounters by specialty, (Table 5) it becomes evident that the knowledge base necessary to manage the majority of those recurring problems is encompassable. The same principle applies to hospitalized patients as well. For example, Rosenblatt and colleagues reported on the rank order frequency of clusters of hospital diagnoses in a probability sample of 651 office-based general and family physicians throughout the US who kept log diaries involving 7830 separate hospital encounters.⁴⁰ Only 15 clusters made up 52% of the encounters. In another study of hospitalized patients of family physicians, more than half of the encounters could be clustered under 12 titles such as atherosclerotic heart disease, normal delivery and diabetes mellitus.⁴¹ Dealing with these familiar problems allows generalists to be experts in the diseases they treat.

Over the past 2 decades, the majority of investigators studying the quality of the family physician's care in the United States have found it comparable to that of their specialty counterparts in a variety of areas including uncomplicated obstetrics and perinatal outcomes,⁴²⁻⁴⁴ congestive heart failure and transient ischemic at-

tacks,⁴⁵ and critical care.⁴⁶ Frequently these patients are managed with assistance from the appropriate specialists as indicated by hospital consultation rates that vary from 25% to more than 76%.^{41,47-49} In addition, family physicians often provide consultation to other specialists.⁵⁰ For instance, 27% of hospital contacts by family physicians in a large multi-specialty group involved consulting on patients hospitalized by other specialists.⁴¹ Also, measurements of quality are closely linked with continuity and comprehensiveness, the hallmarks of family medicine. Franks et al reviewed eight studies that correlate these characteristics with improved outcomes in patients of all ages including higher birthweight, reduced morbidity in children and reduced hospitalization in the elderly.⁵¹ Other studies indicate that quality declines when specialists provide care outside their specialty.^{52,53} Because of their orientation and need for closure, they may order more invasive and expensive diagnostic tests with a greater likelihood of iatrogenic complications and false positive results, requiring even further testing.⁵¹ Furthermore, specialists who spend a disproportionate time providing primary care may find that their expertise diminishes in managing the more complex disorders for which they have pursued intense training.

The variation in practice patterns between the generalist and the subspecialist explains some of the misunderstanding between these disciplines. The consultant sees a spectrum of patients who usually have already been screened, placing them in a different prognostic category. Thus family physicians are likely to deal with patients' headaches differently from a neurosurgeon. For the family physician, the chance of a brain tumor is extremely remote; in fact, it is probably less than 1 in a 1000. For neurosurgeons, however, it is a more likely possibility. Usually, their patients have been filtered through a referral process and have a higher prior probability of a brain tumor. If the family physician approached each patient with headaches with the mind set of a referral neurosurgeon the cost would be prohibitive. This analogy holds for many of the diseases family physicians en-

counter. Consequently, the type of evaluation by generalists and referral physicians is affected by the prevalence of diseases that each treats. And, although there is an overlap, one must be cautious in transposing standards of quality from one group to the other in an uncritical manner. On the practical level, both approaches are necessary to provide quality care to patient populations and family physicians work in a comfortable manner with specialists in a variety of consultative arrangements and within group practices and managed care programs throughout the country. Enhanced by this perception of quality, the demand for family physicians far exceeds their availability.

Conclusion

Much of human endeavor seems to consist of balancing the dichotomy between reduction and synthesis. Considerable medical progress has resulted from breaking down challenging problems into their components. We have made great strides in technology and impressive scientific discoveries. But this approach, of value in furthering the understanding of disease, often, by itself, is inadequate for the care of individual patients. As concluded by numerous committees over the years, we are in danger of losing the humanistic aspects of medicine, costs are out of hand, and, frequently, patients feel lost, searching from specialist to specialist. Family medicine responds to these concerns, and, in so doing, provides the balance and harmony to medical care that has been disrupted over the past 5 decades. Furthermore, as medical knowledge expands in ways we can hardly imagine over the years ahead with ever increasing technological advances, complexity, and subspecialization, the need will be even greater for generalists to integrate those disparate components of medicine. It is important that these physicians be well trained clinicians relating to other specialists from a position of mutual respect, who will provide continuous, comprehensive and personal care for patients within the context of their family, culture and values. In this manner, family physicians, secure in the knowledge of the quality of their work, will continue to

find special meaning in their lives through participation in a vocation with roots as deep as human history and, yet, as modern as today's latest scientific discovery.

Acknowledgments

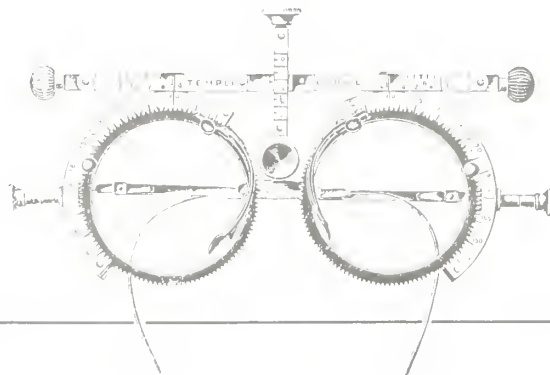
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Carrot Juice Xanthoderma: An Orange Patient with Multiple Myeloma

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A patient presenting with yellowish discoloration of the skin is often thought to have jaundice because of excessive bilirubin deposition. However, other causes of yellow skin discoloration must also be considered if the bilirubin levels are within normal limits. These include hypercarotene-
mia, lycopenemia, and drug effects. We present a patient with multiple myeloma whose yellow-orange skin discoloration was due to excessive intake of carrot juice and not hyperbilirubinemia. We have reviewed the literature especially concerning unusual causes of skin discoloration in patients with multiple myeloma.

The patient is a 66-year-old black woman admitted to Miriam Hospital, Providence, RI in January 1991 with progressive bilateral hand pain and yellow palms. She was in good health until 2 years before admission when she began experiencing low back pain. At that time X-rays at another hospital revealed a lumbosacral spine fracture. A work-up for multiple myeloma ensued. A bone marrow biopsy demonstrated 7% plasma cells. This suggested myeloma, and a repeat biopsy was sought. The patient was then lost to medical follow-up.

For 18 months she saw a chiropractor intermittently and obtained some pain relief. She did well until the sum-

mer before admission when she presented to a different hospital with pain in her lower extremities, fatigue, and weight loss. A CT scan of the spine revealed lytic lesions of the T12 and L1 vertebral bodies. The patient again refused a bone marrow biopsy and was again lost to medical follow-up.

About 1 month before admission the patient began to experience pain in her left hand. The pain lasted throughout the day and intensified at night. She found slight relief with acetaminophen. The pain also was relieved somewhat by shaking her hand as it dangled from a chair. About 1 week before admission the pain began to involve her right hand as well. She was no longer able to perform her activities of daily living and sought medical attention as a result.

The past medical history was significant only for a remote history of hypothyroidism for which she took no medication. The only surgical history was a tonsillectomy at age 18.

The patient was a Jehovah's Witness who did not smoke or drink. She also strongly believed in holistic and organic medicine. She had become a vegetarian several months before admission and had only recently begun eating meats again. In further discussions with the patient it was learned that she had been drinking large quantities of carrot juice as part of her "organic therapy" for several months before hospital admission.

The physical exam revealed a thin woman in no apparent distress. She appeared younger than her age. Skin exam showed no generalized jaundice but palms and soles were a yellow-orange color that could not be washed

A patient with multiple myeloma presented with xanthoderma, yellowish discoloration of the skin. Its cause was determined to be excessive carrot juice ingestion. We describe this patient fully and review the literature as it pertains to etiologies of xanthoderma, especially those associated with multiple myeloma.

or rubbed off. Sclerae were non-icteric. Lungs were clear. Cardiac exam revealed a II/VI systolic ejection murmur radiating to the aortic region and carotids. The abdomen was without palpable masses or hepatosplenomegaly. The spine was not tender to palpation. The neurological exam was within normal limits, except for mild left hand weakness and demonstration of Tinel's sign bilaterally.

Laboratory studies showed a hemoglobin of 5.5 g/dL, hematocrit of 16.6%, white cell count of 10,000/mm³ with a normal differential. There was no rouleaux formation of the peripheral smear. Platelet count was 100,000/mm³. The reticulocyte count was 1.7%. The electrolytes were within normal limits; however, the BUN was 27mg% (nl 7-22) and creatinine was 2.9mg% (nl 0.7-1.4). Serum calcium was 11.6mg% (nl 8.7-10.5) and phosphorous was 5.1 mg% (nl 2.6-4.4). The liver enzymes and coagulation studies were normal. Total bilirubin was 0.2mg/100ml, and direct bilirubin was 0.2mg/100ml. Albumin was 4.7. A 24-hour urine protein was 12,275 mg, and electrophoretic exam of the urine revealed 2 monoclonal spikes. Urine immunoelectrophoresis

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revealed free kappa light chains that were atypical in electrophoretic mobility. Serum protein electrophoresis showed marked reduction of gamma chains, but a small monoclonal peak at the end of the gamma region.

Radiographic studies revealed diffuse osteoporosis. Osteolytic lesions were noted in the skull, humeri, femurs and possibly the pelvis. No osteolytic lesions were noted in the spine, but compression fractures were present in the lower thoracic vertebrae. A bone marrow biopsy showed over 90% plasma cells.

Discussion

This patient demonstrated typical findings of multiple myeloma including anemia, hypercalcemia, osteolytic bone lesions and characteristic urine and serum electrophoresis findings. Of note in this patient is her presentation of yellow palms and soles with non-icteric sclerae.

Xanthoderma is defined as any yellowish discoloration of the skin. When presented with such a patient a variety of possible causes may be considered.

The major cause of yellow skin discoloration is hyperbilirubinemia.

Bilirubin has a predilection for elastic tissue and therefore is often deposited in the skin and sclerae. The sclerae are often the sites where jaundice is first detected clinically due to their high concentration of elastin. Thus, plasma bilirubin concentration is an important value in determining the etiology of xanthoderma. Skin changes are not usually noted until bilirubin levels rise to about 2.0mg/100ml (normal range is 0.5-1.0mg/100ml).

A second cause of xanthoderma is hypercarotenemia. Excessive amounts of beta carotene can lead to an orange-yellow discoloration, especially of the palms and soles. Green vegetables, carrots, oranges, squash, spinach and some vegetable oils contain high amounts of beta carotene. Beta carotene is absorbed in the intestine where it is converted to vitamin A. However, excess beta carotene is not converted into vitamin A and is instead deposited in fat and the stratum corneum of the skin. Carotenemia often results in xanthoderma involving only the palms and soles, where the stratum corneum is most prominent. Hypothyroidism is a predisposing factor for carotenemia.

Other causes of xanthoderma are

less common than hyperbilirubinemia and hypercarotenemia. Certain drugs may cause a yellowish discoloration of the skin. Most frequently encountered is quinacrine, an anti-malarial drug whose chronic use causes a yellowing of the skin, sclerae and mucous membranes. Other chemicals causing xanthoderma include saffron, santonin, fluorescein, dinitrophenols, tetraol and picric acids and acriflavin.

Lycopenemia is another rare cause of xanthoderma. Lycopene, an isomer of carotene, is found in tomatoes and certain berries. It is similar to carotene in its metabolism but is not converted to vitamin A. It also stains skin in a manner similar to carotene, involving the palms and soles.

An interesting case report¹ discusses an elderly multiple myeloma patient with xanthoderma and normal-colored sclerae. This woman had an intense and unusually bright-yellow discoloration of her skin with non-icteric sclerae. The yellow skin discoloration was not confined to only her palms and soles. She also had xanthotrichia, yellow discoloration of the hair. The striking xanthoderma without icteric sclerae suggested a non-biliru-

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bin-related abnormality. The investigators discovered a monoclonal IgG anti-flavin antibody. The purified antibody was bright yellow. It was discovered that this antibody binds riboflavin as a hapten. The hapten (riboflavin) bound to the antibody was responsible for this elderly woman's xanthoderma. Thus, riboflavinemia can be added to the differential diagnosis of a patient with xanthoderma.

Our patient's xanthoderma was most consistent with carotenemia. The history revealed an excess intake of carrot juice for several months as a form of "organic therapy." No unusual medications or chemical exposure could explain her xanthoderma. This patient's non-icteric sclerae suggested some cause other than hyperbilirubinemia as a source of her xanthoderma. Bilirubin levels as well as the liver enzymes were within normal limits. (Total bilirubin was 0.2mg/100ml.)

One method to distinguish hyperbilirubinemia from carotenemia is to examine the skin under natural and artificial light. Jaundiced skin from hyperbilirubinemia will be more evident when examined under natural light, while yellowed skin caused by carotenemia will be more visible under artificial light. This phenomenon was reported after studying a 28-year-old woman who acquired carotenemia while on a fad diet consisting of large amounts of yellow, carotene-containing vegetables and multi-vitamins.²

Another case of yellow-orange palms and soles was reported in a 29-year-old man from Liberia who had a history of ingesting large amounts of red palm oil. His mother and his siblings also had a history of yellow-orange pigmentation. It was found that red palm oil, a popular cooking oil in West Africa, is rich in beta-carotene. Carotenoderma is a common occurrence in this part of the world.³

In conclusion, our patient with multiple myeloma and discolored palms and soles demonstrated xanthoderma and not typical jaundice. The history of excessive carrot juice ingestion was an important clue. Discoloration of the sclerae indicates hyperbilirubinemia while involvement of only the palms and soles with non-icteric sclerae is most consistent with hypercarotenemia. Hypercarotenemia and lycopenemia can be diagnosed after

taking a detailed diet history. It is also important to review the patient's medications for their possible role in directly causing skin discoloration (ie, quinacrine) or perhaps indirectly causing skin discoloration through liver toxicity. Finally, although our patient had multiple myeloma, she did not demonstrate the same features as another patient with multiple myeloma with xanthoderma who had an IgG anti-flavin antibody.¹

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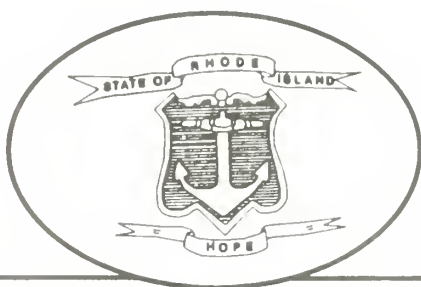
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Patient Education for Screening Mammography: the Unmet Need

The importance of screening in the control of breast cancer is universally recognized.¹ Current US age-specific screening guidelines include:

Women 40-49: Breast physical examination every year and screening mammography every 1 to 2 years.

Women 50+: Breast physical examination and screening mammography every year.

A related national health objective for the Year 2000 reads:

"Increase clinical breast exams and mammography every 2 years to at least 60% of women aged 50 and older."²

The Behavioral Risk Factor Surveillance System, an ongoing telephone survey of RI adult residents, showed that screening rates among women ages 50 and older had reached the national target in 1992, with 60% of women screened as specified (58% of lower income women; 61% of higher income women). Nonetheless, many women still are not screened according to guidelines, primarily because they do not receive screening mammography appropriately.

The Health Belief Model suggests that women's perceptions and the recommendations of their health care providers may affect their propensity for screening.³ For example, the model suggests that women who receive screening mammograms regularly:

- Perceive screening mammography to be safe;
- Perceive screening mammography to be effective in preventing death from breast cancer; and
- Receive regular recommendations for screening mammography from a health care provider.³

Three special surveys of women ages 40 and over have been performed

to monitor women's cancer screening practices and beliefs in Rhode Island. The first, in late 1987, used random digit dialing to interview a statewide sample of 852 women (response rate = 78%). The second, in mid-1989, repeated the 1987 survey (856 interviewed; response rate = 79%). The third, run in early 1991, used reverse telephone directories to interview 828 women (response rate = 70%) residing in low income census tracts with at least 5% black or Hispanic residents (based on the 1980 Census). The Health Belief Model guided the choice of survey questions. Selected results of the surveys have been reported previously.³⁻⁶

Across the three surveys between 59% and 81% of respondents perceived screening mammography to be safe (Figure 1), between 37% and 61% perceived screening mammography to be effective in the early detection of breast cancer (Figure 2), and between 34% and 64% had ever received a recommendation for screening mammography from a health care provider (Figure 3). In general, trends in women's perceptions and providers' recommendations were positive. However, perceptions about screening mammography were less positive among lower income women than higher income women, and lower income women were less likely than others to have had screening mammography recommended to them by a health care provider (Figures 1-3). Overall, the data reveal considerable room for additional patient education, as well as more consistent recommendations from health care providers.

In collaboration with the Rhode

Island community, and supported by the Centers for Disease Control and Prevention, the Rhode Island Department of Health has undertaken the development of a plan for women's cancer screening, to guide the State in this area as it approaches the Year 2000. Primary care physicians, nurse practitioners, and other health care professionals who perform preventive gynecological care, educate patients, and serve as gatekeepers for screening mammography will figure prominently in the planning process and ultimately in the recommendations of the plan itself.

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Submitted by John P. Fulton, PhD, Francis A. Donahue, MA, and Anne C. Jones, MSW, Office of Chronic Disease Prevention and Health Promotion. Health by Numbers is edited by Jay S. Buechner, PhD, and William J. Waters, Jr., PhD.

Fig 1.—Percentage of Rhode Island women ages 40 and older who perceive screening mammography to be safe, by year and family income, Rhode Island, 1987-1991

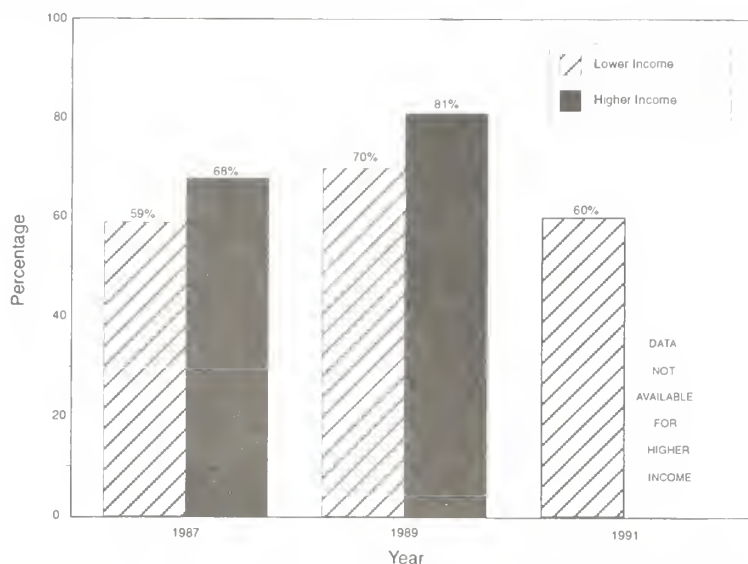


Fig 2.—Percentage of Rhode Island women ages 40 and older who perceive screening mammography to be effective, by year and family income, Rhode Island, 1987-1991

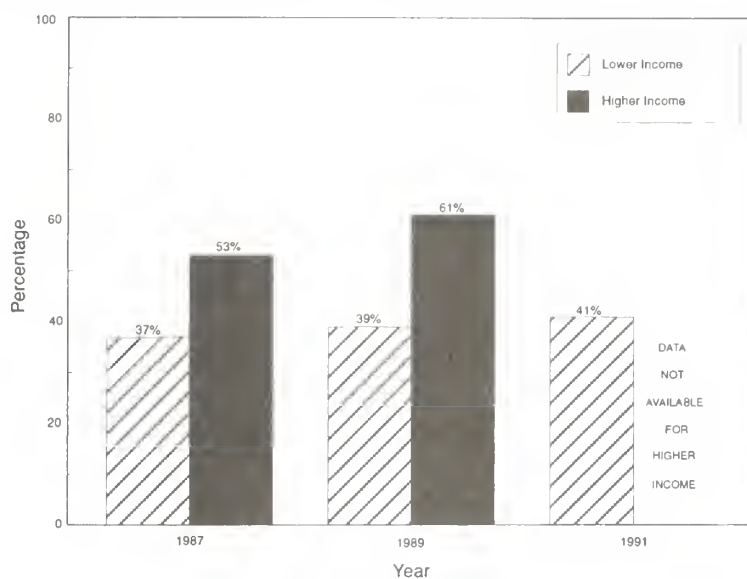
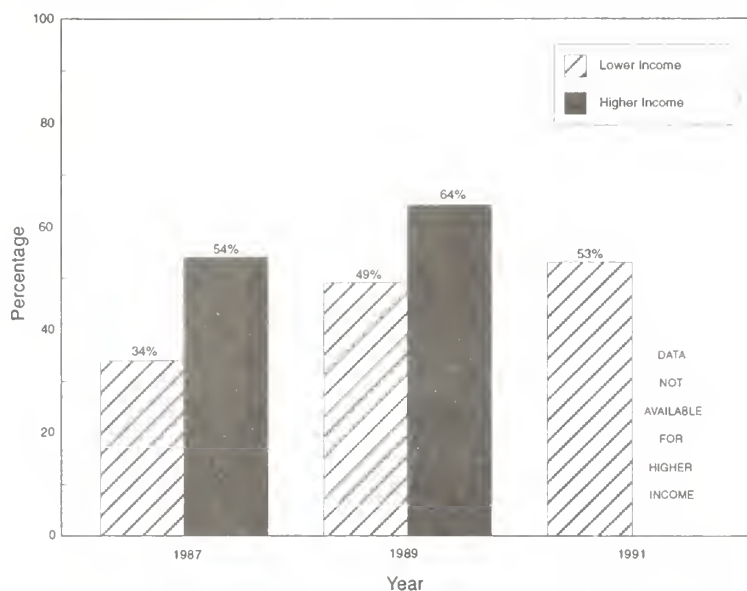


Fig 3.—Percentage of Rhode Island women ages 40 and older who have ever received a provider's recommendation for screening mammography, by year and family income, Rhode Island, 1987-1991



THE RHODE ISLAND MEDICAL JOURNAL

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

90 Years Ago (July 1903)

The lead article, a lengthy and scholarly discussion concerning recent progress in the phenomenon of immunity, is written by Frank T. Fulton, MD, and represents the annual address to the Rhode Island Medical Society. Aside from its length, the article provides the reader with an unusual feature. It is the first article carried by the Journal to offer extensive bibliographic references from both the European and American literature. Fulton begins his discussion with a gentle reminder to the busy practitioner that only through lifelong study can he achieve some connection with and comprehension of the recent advances of medicine. He quotes Virchow: "Day by day do those who are obliged to consume their best energies in the frequently so toilsome and so exhausting routine of practice, find it becoming less and less possible for them not only to closely examine, but even to understand the more recent medical works. For even the language of medicine is gradually assuming another appearance." Fulton appreciates, too, the dramatic changes in the character and curricular content of the United States medical schools at the beginning of the 20th century. The changes, he observes, are "nothing less than marvelous." He points, particularly, to newer techniques in the teaching of methods of treatment, methods of clinical observations and classification of disease. He notes particularly the radical departure in laboratory exercises in bacteriology and pathology taking place in the better

medical schools of this country. His dissertation then dwells upon the newer science introduced by Paul Ehrlich called immunology. During the last half century, he notes, there have been three major developments in the science of medicine, beginning first with the cellular basis of both normal and abnormal function advocated by Virchow; secondly, the contributions of Pasteur and Koch in the development of clinical bacteriology; and thirdly, the immense revelations in immunology, disease resistance and toxicology by numerous research scientists. He dwells particularly upon the experiments of Ehrlich and Metchnikoff, the latter dealing with the new phenomenon of phagocytosis and cellular (in contrast to humeral) immunity. The different kinds of toxins are then reviewed—both those which are easily liberated by bacteria as well as those—called endotoxins—which become effective only after lysis of the bacterium (as in the case of diphtheria and tetanus). The binding actions of various toxins are then discussed, in conjunction with Ehrlich's theory that toxin molecules have two functional elements (haptophores and toxophores). A newer serum component, called complement, is also considered. The paper concludes with a multitude of unanswered questions including: the natural immunity of certain snakes to their own venom; the nature of autolysins in cell death; the production of anti-immune compounds. And the hope that the new experiments in attempting to achieve an anti-epithelial serum to counteract the effects of epithelial neoplasms will achieve success.

A second paper, by F.T. Rogers, MD, discusses myopia and its relation to school life. The author first classifies myopia into four categories: Transient curvature myopia, arising from excessive and close work allied often with poor illumination; permanent curvature myopia, due to structural and pathological changes in the cornea or lens; index myopia, where the index of refraction is increased by changes in the lens (as in cataract); and axial myopia, affecting most profoundly the posterior portion of the globe causing the eyeball to bulge; this is the most common form of myopia, according to the author. In his discussion, the author stresses that myopia is more often a sociological problem than one of diagnosis. He quotes a German proverb, "A blind man is a poor man." Blindness, he observes, is pathologic, poverty is economic, "and it is within our province as physicians and our duty as citizens to prevent as well as we may the increase in the vast army of dependents by reason of defective sight." To what extent is myopia present in the schoolchildren of the United States? A survey in Philadelphia found 88% of school children with defective vision. In Baltimore, 57% of children had defective vision. In the public schools of Providence, 13,500 of 27,000 children have some visual defect, with 1500 suffering from myopia, according to the author. The author concludes with four earnest recommendations to the members of the Medical Society: First, that a commission be formed to determine the precise extent of the problem in the Providence public school system; second, that the school system should set

aside funds to compensate for the medical and clerical work entailed in conducting such a comprehensive survey; third, the teachers should be instructed in methods of testing visual acuity; and fourth, that accurate records should be maintained on each child, with vision testing results recorded at yearly intervals.

50 Years Ago (July 1943)

The lead contribution is a paper by Alexander T. Martin, MD, concerning the recognition and management of rheumatic fever in children. The author estimates that about 1% of the adult work force in the United States suffers from some aspect of rheumatic fever and that the disorder causes about 40,000 deaths per year. In the school age population, he estimates that there are about 200,000 cases of rheumatic heart disease and that this disorder is the major cause of death in this country, in those between the ages of 10 and 14 years. With this background, the author then outlines the various signs and symptoms (cardiac, systemic, cerebral, or synovial) which should alert the practitioner to the onset of rheumatic fever. He discusses the confusing overlap between the polyarticular manifestations of rheumatic fever and so-called growing pains. Finally, he outlines measures to be taken in the continuing treatment and management of a child with verified rheumatic fever, including the use of prophylactic sulfonamides.

Anthony V. Migliaccio, MD, discusses the role of extraperitoneal cecostomy in the decompression of the obstructed colon. The author reviews the anatomy of the abdomen, particularly the reflection of the peritoneum in relation to the cecum. After a brief consideration of the surgical approach and a review of a few cases, the author emphasizes the one fault of this procedure: the inability to inspect the abdo-

men. Hence, he advises, the procedure should be limited to those neglected cases coming to the hospital with distension and signs of toxicity.

Paul C. Cook, MD, discusses leukopenia in infections. He defines leukopenia as a white count of less than 4,000. The article outlines the various causes of reduced white cell counts (eg, decreased production, leucocyte loss as in empyema, accelerated leucocyte destruction, redistribution or sequestration of cells in the vascular channels as in allergic reactions, or extracorporeal infiltration of white cells as in certain forms of leukemia).

Notes from the Rhode Island Medical Society summarize the 15-minute radio talks regularly offered by the society on radio station WPRO every Sunday afternoon since 1938.

The Committee on Necrology reports 13 deaths of physicians in the preceeding year, including one in military service.

A small footnote on tetanus immunization in the military population indicates that since 1941 when the current tetanus immunization program was adopted for all military personnel, there have been but four cases of clinical tetanus, none of whom having been previously immunized.

25 Years Ago (July 1968)

Milford O. Rouse, MD, president of the American Medical Association, is the author of an article on nervous indigestion. After a brief discussion on the nature of neurosis, and the diagnosis and treatment of nervous indigestion, the author turns his attention to the art of medicine. He concludes: "The average general practitioner or internist is inclined to feel that he does not have the time that, at first glance, he thinks will be necessary to devote to a patient with gastric neurosis. Interesting studies have been made, how-

ever, which show that the total time consumed in working to a successful completion of a case of gastric neurosis is really much less than that spent in countless office visits necessary to care for the inadequately treated neurotic patient. It is in the province of every physician to render a real service to his friends and patients by being willing to take the time and the interest to solve the problem. Not less of the science of medicine, but more of the art, is needed."

James L. Goddard, MD, commissioner of the Food and Drug Administration discusses patterns of legislative and administrative change in the research, regulation and communication concerning both established and new drugs. He strongly advocates the establishment of a compendium of drugs within the United States.

Newer methods in the rapid and efficient care of the battle-field wounded are discussed by Jack Penn, FRCS, in a paper reviewing newer traumatological procedures in the June, 1967, Israeli-Arab War.

A report, prepared by the Legal Division of the American Medical Association, discusses the present status of medical malpractice suits.

The editorials discuss the nursing crisis, the newly established FLEX (Federation Licensing Examination) licensing test, aeromedical evacuation procedures, milk intolerance, pulmonary home care, a fee moratorium, and the Brown medical digest. This editorial takes note of a biomedical structure taking shape on the Brown University campus on Meeting Street and the fact that Rhode Island's practicing physicians have as yet had little contact with "the yeasty ferment of this new enterprise." The last editorial, entitled *Frankenstein*, notes with some apprehension that there are said to be more than 40,000 computers in the United States, and then gives examples of such machines going berserk.



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Books:

2. Hollingworth JW. *Local and Systemic Complications of Rheumatoid Arthritis*. Philadelphia, Pa: Saunders; 1968.

Book Chapter

3. Epstein WL. Erythema nodosum. In: Samter M, ed. *Immunological Diseases*, 2nd ed. Boston, Mass.: Little, Brown; 1971;2:944-951.

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose response study. *Clin Cardiol* 1991;14:146-151

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Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus

WARNINGS

Liver Enzymes: HMG CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis, hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin, the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin

Homozygous Familial Hypercholesterolemia Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle

Antipyrene: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids 1 hour prior to PRAVACHOL (pravastatin sodium), cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitals, converting enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin

Endocrine Function: HMG CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a >50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2 year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose dependent and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye-Hardner gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/– mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation) in rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo

The following effects have been reported with drugs in this class

Skeletal: myopathy, rhabdomyolysis

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting

Reproductive: gynecomastia, loss of libido, erectile dysfunction

Eye: progression of cataracts (lens opacities), ophthalmoplegia

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS)

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSEAGE

There have been no reports of overdoses with pravastatin

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required

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Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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Rhode Island **MEDICINE**

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Volume 76, Number 8



Depression



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COMMENTARIES

The Taxonomy of Depression

Emotional depression seems to be a universal affliction. Like taxes and mythology, no society has been without it. To the unaffected, depression sometimes seems appropriate, as in grief following the loss of a loved one; or sometimes inappropriate, as with intractable melancholy. Depression may be transient like a passing cloud, or it may cling tenaciously for years. No sharp threshold separates the socially acceptable human reactions from those sadnesses without cause that virtually all societies recognize as being pathologic; nor have any objective laboratory tests been devised to distinguish one kind of depression from another. Depression persisted, historically, as something more, yet often less, than conventional disease: a burdensome, inconsolable despondency that is often destructive, yet without any obvious structural substrate.

The perplexities associated with this intensely human affliction, however, did not prevent strikingly different interpretations as to its cause; where in the human body it originated; whether it represented a human burden shared to some degree by all; a human disease; or perhaps a spiritual inadequacy.

Our predecessors rarely have been silent on depression. Commentary speculating on its nature and dynamics may be readily found in medical or theological documents, in widely separated cultures, throughout the ages. The names given to depression by these writers had not been randomly selected. Instead, they reflected the prevailing views on the etiology, the anatomic loci of involvement and what was then believed to be the crucial symptom of depression. These diagnostic names included: melancholia, acedia, tristimania, amenomania, lype-mania, hypochondriasis, vapours, mopishness, erotomania, angstmelanchol-

ie, nostalgia, neurasthenia, endogenous depression, and manic-depressive insanity. Depression, or melancholy, also generates an impressive number of nearly equivalent words in the vernacular vocabulary. Roget lists 34 synonyms for "melancholy" alone.

The Greeks had a word for this despondency: *melancholia*, which in the Hippocratic writings, was employed to describe a human with excessive sadness, without fever or head injury, exhibiting restlessness, loss of appetite, disinterest in life, sleeplessness, perhaps anxieties and sometimes delusions or at least distortions of reality. The word melancholy means black bile (in Latin, *atra bilis*), a substance of dubious origin representing one of the four elemental humors of classical Greek pathophysiology (the other three being blood, yellow bile and phlegm). That no one had ever demonstrated black bile did not prevent 3 millennia of medical authors from talking authoritatively on black bile imbalance as the fundamental cause of depression. Not until the 19th century was the medical profession weaned from this curious thought.

Most Classical writers acknowledged that the disorder was not rare. In the abundance of encountered cases, many of them distinguished between those with active melancholia and those appearing normal but encumbered with a melancholic temperament, suggesting that the latter were latent melancholics just waiting for a precipitating agent. Indeed, Aristotle notes: "Why is it that all those who have become eminent in philosophy or politics or poetry or the arts are clearly of a melancholic temperament?" In the belief that melancholia could be provoked in those susceptible to it, some authors strove to identify the provoking factor(s). By Galen's day, most agreed that melancholy was brought on by suppression of menstruation in women or hemor-

rhoidal flux in men.

Therapy for depression was rarely specific. After the acute phase, Soranus advocated a light diet, frequent baths, massages with aromatic oils, no blood-letting or purging, walking and mental exercise (eg, listening to the discussions of philosophers, "... for by their words, philosophers help to banish fear, sorrow and wrath.")

The late Roman and medieval medical writings contributed little more. Melancholy, like Gaul, was divided into three forms, the third variety closely associated with hyperactivity of the gastrointestinal tract, colic and excessive flatulence (the "windy melancholy" of English literature).

By the 4th century, depression was viewed somewhat differently—or at least different aspects of depressed behavior were now being emphasized. These newer behavioral components of depression included a chronic indifference to daily responsibilities, pathological idleness, lassitude and a world weariness. The Latin word, *acedia*, or its English equivalent, sloth, was applied to this face of depression. And because such feelings of irresponsibility and sloth inevitably prevented certain monks from investing themselves fully in their faith, Cassian declared acedia to be one of the eight cardinal sins. A century later, Gregory reduced the number to seven, incorporating acedia into dejection as a mortal sin. One 16th century physician disagreed: "If our spleen or hypochondria send up such melancholic fumes into our heads as move us to sadness and timorousness, we cannot justly call that vice."

Although the leaders of the Reformation also concurred on the corrupting force of willful idleness, melan-



choly gradually returned to its secular state by the early 17th century. Elyot, who had studied medicine, describes depression as follows: "There is nothyng more enemye to lyfe, than sorrowe, called also hevynes, for it exhausteth bothe naturall heate and moysture of the bodye, and dothe extenuate or make the body leane, dul-leth the wytte, and darkeneth the spir-ites, letteth the use and judgement of reason and oppreseth memorye . . ."

Harkening back to the Greco-Roman belief of a special form of melancholy that affects the functions of the abdominal organs, many renaissance writers conceived of a pathogenic sequence starting in the spleen, creating corrupting vapors that ascended to the head resulting in unrelenting sadness. The viscera below the chest were called the *hypochondria* (ie, below the cartilage) and the disorder, *hypochondriasis*. Willis (he of the Circle) declared melancholy to be a disorder of blood leading to a "Melancholick foulness in the Spleen." Indeed by the 18th century, melancholy was sometimes called the "English Disease", or "The Vapours" or merely "Spleen." In the past 3 centuries the meaning of the word hypochondriasis has drifted from its original intent signifying a specific form of melancholy with enteric components; to an excessive concern with one's illness; and then to its present connotation: a morbid preoccupation with ill-defined or imaginary disorders.

The "vapours," now reduced to a comic curiosity of the British stage, had once been the term used to describe depression particularly in women. Addison, in 1711, says about melancholy: "... we must ascribe it to the Spleen which is so frequent in men of sedentary tempers, as well as the Vapours to which those of the other sex are so often subject."

Robert Burton's *The Anatomy of Melancholy* described (and popularized) yet another form of depression, which he called love-melancholy, just in time for a generation of British and German writers to declare it to be of epidemic proportions. Burton's text also provides the reader with an awesome classification of melancholia etiologies including those mediated by witches; those caused by an excess (or defect) of venery; idleness; solitari-ness; vehement desires (including

ambition and covetousness); love of learning; and stopped "hemrods."

The 18th century added a new dimension to our understanding of melancholia. Samuel Johnson, himself a sufferer of chronic depression, wrote extensively on the burdens, darknesses and terrors of his illness. In his great dictionary, he defined melancholy as follows: "... a disease supposed to proceed from a redundance of black bile; but it is better known to arise from too heavy and too viscid blood: its cure is in evacuation, nervous medicines and powerful stimuli." It was Johnson, incidentally, who first used the word depression to describe his personal illness.

A century later, a new term, neurasthenia, was applied to melancholy: it was defined as an exhaustion of spirit, often associated with phobias and a pervasive lack of vitality. In World War I, neurasthenia and shell-shock were synonymous terms.

Freud called attention to the core similarities between melancholy and mourning, and considered the former as a form of mourning superimposed upon a disturbance of self-regard. It was his contention that the true object mourned, in the melancholic person, was deeply suppressed.

One further term for depression, nostalgia, needs to be considered. In the late 17th century Hofer published his treatise on homesickness (*Heimweh*) and coined a word from Greek roots (*nostos*—return to the home-land; and *algos*—pain) to describe this form of excessive reaction to a separation from one's home. The meaning of nostalgia has also changed in the past few centuries assuming, by the 19th century, a more gentle, less disease-oriented texture. Longfellow said it is:

A feeling of sadness and longing,
That is not akin to pain,
And resembles sorrow only
As the mist resembles rain.

Twenty-four centuries of speculation, ferment and pronouncement have still not revealed for us the full roots of depression. The therapist asks: "Where is the fault?" And the melancholic victim asks: "Who can I blame?" From whatever cause, and by whatever name, depression remains an oppressive burden for the afflicted. Milton, perhaps disclosing his feelings, wrote:
... loathed Melancholy,
of Cerebus and blackest midnight born,

In Stygian cave forlorn,
'Mongst horrid shapes, and shrieks and
sights unholy.

Stanley M. Aronson, MD

The Naming of Drugs

If no new drugs were invented, drug companies would have no need to devise new names for their evolving products. But for both economic and humanitarian reasons the number of new products reaching the marketplace increases each year; and the pharmaceutical companies therefore are obliged to provide unique names for their newly developed medications. Using the generic or chemical name, of course, would deprive their particular brand of any individuality or market visibility. Accordingly, the companies invest much energy in devising novel names with an enduring quality and may even suggest their purpose.

Chosen, nongeneric names for medicines fit several categories: Names that reflect molecular structure; names that paraphrase the illness to be treated; geographic names; names that exploit certain Latin or Greek roots, particularly those that hint at peace, aliveness or utopian existence; names that symbolize the manufacturer; and names that hint at the goals of therapy.

If they are like the auto manufacturers, the drug companies provide tight security for their name-selecting research. No pharmaceutical companies had been consulted as to the etymological origins of the drug names considered below. Thus, we are assuming, for example, that the drug **Librium** was derived from a shortening of the word equilibrium, suggesting that its use will therefore bring some balance and harmony to the life of its user. Of course it is equally plausible, but unverified, that the drug company had a senior pharmacologist named Lester I. Bronson who decided to name the psychoactive agent after himself. Some of the trade name derivations below, then, are pure speculation.

The names of medications vary from the self-evident to the abstruse. The provenance of **Proventil** (a bronchodilator), for example, is quite obvious, as are names such as **Antivert** or **Topicort** or **Cerumenex**. Some, such as **Azmacort**, are equally self-evident but may occasion a momentary cringe.

A few names serve to remind the physician of the manufacturer's name (eg, **Rocephin**, Roche's cephalosporin; **Ledercillin**, Lederle's penicillin; or Syntex' naproxen sold as **Naprosyn**.)

One of the more common name-generating mechanisms extracts the first (or last) syllables of the generic description. Thus, antiseptic benzocaine solution (used as a surface anesthetic for painful teeth) becomes **Anbesol**. A distillate of pregnant mare's urine becomes **Premarin**; and haloperidol evolves into **Haldol**.

Yet another technique used is the incorporation of instructions into the name, as with the many products ending in "bid" (eg, **Lithabid**, **Macrobid**, **Spectrobid**). The orally active antipsychotic agent, pimozide is sold under the trade name of **Orap**.

The names of institutions—or their locations—may also become part of a new medication name. **Fiorinal**, for example, is said to be named after Montefiore Hospital where this drug-combination was first devised for the treatment of migraine. **Nystatin** is named after the NY State institution where it was first investigated.

The most imaginative drug names, however, seem to be found among the psychotropics, particularly the antidepressants. The names hint at greater peace and tranquillity for their users. We encounter such labels as **Halcion** (*Alcyone*, in Greek legend, was a mythical seabird that had the power of calming the raging seas); **Atarax** (the Greek word for calmness and freedom from anxiety); **Vivactil** (Latin, *vivus*, meaning aliveness); and **Equanil** (Latin, for composure under tension). Some of the antidepressants, such as **Elavil** and **Endep** are more obviously derived. **Sinequan** (presumably from the phrase *sine qua non*, without which, none) seems a bit presumptuous. A few names require some intimacy with neurochemical function. **Limbitrol**, for example, most likely seeks to describe a medication capable of exerting limbic system control. The etymologic origins of many psychoactive agents trade names remain obscure. **Valium**, for example, may have been named after the Latin *valere*, to be strong, to be healthy. The *-ium* suffix, by convention applied to chemical names denoting elemental status (eg, barium, sodium, lithium), gives the

drug an even more imposing place in the pharmacopoeia. An agent such as **Xanax** defies easy analysis. In its favor, though, is its neat palindromic symmetry and the prominence of the letter "x" adding a metaphysical aura.

Finally, there are proprietary drug names that are difficult to analyze. Some of late seem to incorporate the letter "z" into the name such as **Prozac**, **Clozaril** and **Zoloft**. Like the names

of some Japanese auto models, they may be pure verbal inventions designed to elicit some sought-after response from a well-spring that goes deeper than our etymological roots.

The obvious thing to do is to inquire of the drug companies how they devised their product names, but this would deprive us of the joy of idle speculation.

Stanley M. Aronson, MD

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Overview of Depression: Chronicity, Recurrence, Morbidity and the Need for Maintenance Treatment

Martin B. Keller, MD

In the late 1800s, Kraepelin postulated that depression should be thought of as a psychiatric disorder in which discrete episodes of illness alternated with clearly defined "well periods," during which patients returned to their previous state of health. Until the late 1970s, this outcome characteristic was one of the ways that depression was differentiated from schizophrenia, in which the course of illness was observed to be chronic and unremitting.¹

For over a decade research and clinical observation have shown that patients with depression have a significant likelihood of experiencing relapse, recurrence, chronicity, and residual "subsyndromal" symptoms between full-criteria episodes of illness. In addition, depression is one of the most common psychiatric illnesses. Data gathered by the Epidemiological Catchment Area Study indicated an 8% lifetime prevalence for depression in its general population sample.² Death from suicide is markedly increased among depressed individuals, and the risk of death by suicide is 15% for people hospitalized for depression.³⁻⁶ It is, therefore, of great importance that all physicians be made aware of the risk that major depression may become chronic or recurrent, and of the need to continue to treat patients with this disorder even when symptoms have abated to subsyndromal levels, and to consider maintenance treatment after full recovery.

Our understanding of depression treatment is consistently evolving and

expanding. In preparation for the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, the nomenclature on psychiatric disorders sponsored by the American Psychiatric Association, a mood disorders field trial task force was developed to assess the relationship between major depression, dysthymia, minor depression and depressive personality disorder. With all the emerging research data in the area, it became clear that there were some problems with the *DSM-III-R* Mood Disorders section. For example, the severity and course criteria for major depression and depressive personality disorder is unclear, and in the clinical samples used, more than 80% of the subjects with dysthymia also met criteria major depression.⁷ The five sites involved in the field trial are Butler Hospital/Brown University, Virginia Commonwealth University, Payne Whitney Clinic at Cornell University, State University of New York at Stonybrook, and University of Texas Medical Branch at Galveston. The field trial was completed in late 1992 and the data soon will be submitted for publication.

The preliminary findings have had a significant impact on redefining the depressive disorders for *DSM-IV*, which will be published in late 1993 or early 1994. Moreover, substantial changes will be made in the definition of dysthymic disorders to better differentiate it from major depression. On the basis of this research, it has been agreed that course modifiers are necessary to provide a complete and accurate clinical picture of depression. Because understanding course is essential to the treatment of an illness, it is important to document and understand various patterns that the illness may take. For example, all patients

... depression is one of the most common psychiatric illnesses. Data ... indicated an 8% lifetime prevalence for depression.

with major depression will be specified as being single episode or recurrent and the frequency and temporal relationship of episodes of dysthymia and major depression will be described.

Chronicity

Since its inception in 1974, the National Institute of Mental Health (NIMH) Collaborative Study of the Psychobiology of Depression (CDS) has consistently provided evidence that depression is a chronic and recurrent condition. The CDS, which is ongoing, is a 17-year, longitudinal prospective study of 965 depressed patients and 3500 of their first-degree relatives. The CDS has provided us with a unique opportunity to prospectively observe the course of depression. Specifically, we are learning with precision, whether and for how long symptoms remit during a multi-year illness, and whether patients actually "recover," if recovery is defined as a return to the pre-depression state. The Collaborative Study examined the course of illness in depressed probands at 6-month intervals for 5 years and thereafter at annual intervals for a minimum of 10 years on all subjects.⁸ At

ABBREVIATIONS USED:

CDS: Collaborative Depression Study

DART: Depression Awareness, Recognition and Treatment Program

DSM: Diagnostic and Statistical Manual of Mental Disorders

IPT: Interpersonal psychotherapy

MAOI: Monamine oxidase inhibitor

MDD: Major depressive disorder

NIMH: National Institute of Mental Health

RDC: Research diagnostic criteria

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each interval, data suggest that a significant percentage of the patients remained chronically ill, despite the previously widely held clinical belief that depressed patients tend to make complete recoveries from acute depressive episodes.

In 1984, for example, a 2-year follow-up of 97 patients with the diagnosis of major depressive disorder found that 21% of the subjects had not recovered during the 2 years. Given that the median duration of illness *before enrollment* in the study was approximately 1 year among the non-recovered subjects, these data suggest that a significant portion of the subjects were chronically ill for 3 years.⁹ Factors that were found to predict a slower time to recovery were longer duration and increased severity of the index episode, a prior history of a non-affective psychiatric disorder (suggesting that the depression in these subjects was secondary), lower family income, and being married during the index episode.⁹

The cumulative probability of recovery for 431 Collaborative Study subjects who entered the study in an episode of major depression, with no history of mania, hypomania, schizoaffective disorder, underlying minor depression or chronic intermittent depression (defined as dysthymia in *DSM-III* and *DSM-III-R*) was 88% after 5 years of prospective follow-up.⁸ Probabilities were calculated for intervals ranging from 1 week to 5 years, and showed that the chances of recovery from major depression were the highest within the first 6 months following entry into the study. For example, the probability of recovering within 1 week of entry into the study was 3%; by 4 weeks, the probability was 19%; by 8 weeks, probability was 31%; within 13 weeks, 41%; within 26 weeks, 54%. The probability of recovery from major depression within 1 year was 70%; within 2 years, 81%; within 4 years, 87%; and within 5 years, 88%.⁸ The longer subjects were depressed, the less likely recovery became, as suggested by the fact that only 18% of the probands still depressed after 1 year of follow-up recovered between years 1 and 5, while 54% recovered during the first 6 months after enrollment in the study.

Six factors were found to be signifi-

cantly associated with a chronic course. They were: long episode duration before entry into the study; admitting research center; marital status (married); inpatient hospitalization status at intake; and low family income; RDC secondary-unipolar subtypes (which include schizophrenia, panic, obsessive-compulsive, phobic, schizoaffective and drug use disorder, alcoholism, anorexia, and organic brain syndrome).⁹

The majority of patients who did not recover during the 5 years of follow-up experienced sub-criteria symptoms of depression most of the time; their illness resembled chronic minor depression or dysthymia with episodes of major depression, rather than major depression alone.⁸

... a significant percentage of the patients remained chronically ill, despite the previously widely held clinical belief that depressed patients tend to make complete recoveries from acute depressive episodes.

Among patients who do recover from acute episodes of major depression, relapse is frequent, although the risk of relapse tends to decrease the longer the patients remain well. In a 1983 study of 141 depressed Collaborative subjects who recovered from the index episode of illness, we found that the cumulative probability of relapse was 22% after 1 year of follow-up (67% in the secondary patients).¹⁰ Patients who had previously had three or more episodes of major depression had shorter times from recovery to relapse than did patients who had experienced fewer than three episodes before entering the study. In first-episode patients, being older and having had a preceding non-affective psychiatric illness predicted a significantly shorter time to relapse.

Data, published in 1986 on 101 patients who recovered from the index episode of depression and subsequently relapsed, examined the length of the first prospective episode (ie, the first new episode of depression observed during the follow-up period).¹¹ Among

patients who relapsed, the Kaplan-Meier estimate of the probability of remaining ill for 1 year or more was 22%. This rate of chronicity is similar to that found among patients during their index episode. Predictors of a prolonged time to recovery during the first prospective episode were: 1) a longer index episode of major depression; 2) older age at relapse; and 3) lower family income. Neither number of previous episodes, gender, treatment status, RDC subtype, severity of the index episode, nor the presence of pre-existing dysthymia predicted the length of the first prospective episode. On the basis of the 21% rate of chronicity following 1 year of follow-up, it was determined that a long prior episode, older age, and low family income were predictive of chronicity in the first prospective episode. A non-significant trend toward slower recovery was found in patients who were divorced or separated vs those who were married or single.¹¹

Recurrence

A number of other researchers have investigated the frequency of recurrence and chronicity in major depression.^{12,15,16} Their data confirm that a significant percentage of depressed patients experience multiple episodes or lengthy episodes without a return to the "pre-depression" state of well-being. This differs from Kraepelinian theory that depression consisted of discrete episodes of illness alternating with clearly defined well periods.¹

Angst, for example, found that 15% to 20% of depressed patients develop chronicity, and that up to 20% commit suicide.¹² A 20-year follow-up by this author indicated that depressed patients spend as much as 20% of their lifetime in depressive episodes. Angst's "Zurich study" of depression followed a cohort of individuals for 10 years, tracing the disorder's epidemiology and course.¹³ Over the course of a single year, about 30% of the depressions Angst observed were "monophasic," and over 10 years, 25% of patients had only a single episode. This data suggests that the majority of depressions, at least in the Zurich sample, consisted of multiple episodes. Indeed, Angst claims that "today we can assume that 75% to 80% of de-

pressive cases are recurrent." He notes that socio-demographic variables such as race, social class, education level, marital status, religion, intelligence, gender, age, positive family history of depression, and growing up in a "broken home" do not predict outcome in depressive episodes.

Double Depression

Another factor that strongly influences the course of depression is the presence of "double depression." This phenomenon has been defined as the concurrent presence of both dysthymia and major depressive disorder, in which acute major depressive episodes appear to be "superimposed" upon the underlying chronic depression.¹⁴ Before the Collaborative Study's investigations into double depression, Rounsaville and colleagues reported that, in a sample of 64 depressed patients, only 34% met criteria for major depression only.¹⁵ The rest all suffered from some form of chronic minor depression: 36% had intermittent depressive disorder, 14% had cyclothymic personality, and 16% had labile personality. Akiskal also reported the presence of "chronic characterological depression" with superimposed major depressive disorder in 55% of depressed patients.¹⁶

The presence of "double depression," most simply put, means that patients recovering from acute major depressive episodes rarely return to a pre-illness state of well-being. Dysthymia is, by definition, chronic; *DSM-III-R* criteria for the disorder require depressed mood that is present for at least 2 years' duration, although with symptoms less severe than those of major depressive disorder.⁷

An analysis of the first 101 depressed patients enrolled in the Collaborative Study revealed that 26% of patients had an underlying chronic depression of at least 2 years' duration.¹⁴ In 20 of those patients, the underlying minor depression met criteria for dysthymia. Patients with "double depression" tended to be female, older than 30, and single, although none of these factors were statistically significant.

One-year follow-up revealed that the patients with double depression were more likely to have recovered

from their acute episode of major depressive disorder than were patients with major depressive disorder only (88% vs 69%). However, the majority of these patients (58%) did not recover from their underlying, chronic minor depression. Analysis of the length of chronic depression before study intake indicated that 96% of the "double depressed" patients had chronic minor depression lasting 3 years or more; 73% had been ill for 5 years or more, and 42% had been ill for 10 years or more. Follow-up also showed that patients with double depression had a higher rate of relapse than patients with major depression only.¹⁴

A subsequent 2-year follow-up of 316 Collaborative patients identified 80 patients with "double depression."¹⁷ The longer follow-up period allowed a more in-depth examination of the course, predictors of course, and sociodemographic features of the double depressed patients.

It is imperative that clinicians who treat depressed patients remain aware of the perniciousness of the illness and of the many effective options available for its treatment.

Again, time to recovery from the index episode of major depression was shorter in double-depressed patients; among those still ill at 1 year, there was an 82% probability of recovery during the 2nd year, compared with only 29% for patients with major depression only. However, while the double depressed patients recovered from acute major depression at a median of 13 weeks from entry, their recovery from chronic minor depression had not been observed after 104 weeks of follow-up.¹⁷

At 2-year follow-up, 97% of patients with double depression had recovered from the index episode of major depression, vs 79% of the patients with major depression only. However, 58% still had not recovered from the underlying dysthymia.

The three variables that were found to predict shorter time to recovery in all patients were shorter duration of the index episode of depression, more acute onset of the index episode, and

less severe Hamilton Depression Score. Patients with double depression had shorter and more severe episodes of major depression. They were also more likely to relapse than patients with major depression only.¹⁷

When the course of illness of the two groups was followed for 6 months, it was found that more double depressed than MDD-only patients failed to recover (75% vs 32.4%). In addition, 29% of patients with double depression developed RDC definite or probable hypomania during the follow-up period, as opposed to 8.6% of the patients with episodic major depression. Overall, patients with double depression reported higher mean levels of depression and poorer global functioning, as measured by the Beck Depression Inventory and the Social Adjustment Scale.¹⁸

These data suggest that double depression is relatively common among patients with major depression, and that the presence of chronic underlying minor depression has clinical and prognostic significance. Patients with double depression recover from major depressive episodes quickly, but their recovery from chronic minor depression is slow. Those who do recover tend to relapse more frequently and rapidly. In addition, the longer these patients remain chronically ill, the more likely they are to relapse. Clinicians treating "double depressed" patients should institute intensive somatotherapy to prevent them from entering a state of chronic illness.

Undertreatment of Depression

As noted above, the Collaborative is a naturalistic study; therefore, no attempt was made to control the type or duration of treatment received by the subjects. However, information on treatment received was gathered. While it is not possible to infer a causal link between the treatment data and the high rate of chronicity, relapse and recurrence found in our sample, it is clinically important to note that most of the Collaborative subjects received inadequate treatment for their depressive episodes, both before and after they were enrolled in the study.

Treatment data was gathered on the first 217 depressed subjects entering the Collaborative. These data focused

on the treatment, if any, that the subjects received while they were in the community, before enrolling in the study. It was found that most of the subjects had received psychotherapy (67%) or anti-anxiety medications (55%).¹⁹ Only 34% of the patients received antidepressant medication for 4 consecutive weeks, and only 3% received the most intensive possible dose. Most subjects who did receive antidepressants received only the equivalent of 150 mg of imipramine hydrochloride for 1 month. A subsequent study of treatment received by 338 Collaborative patients during the first 8 weeks following their enrollment found similarly low levels of treatment.²⁰

Subjects were stratified by inpatient or outpatient status. Among inpatients, 78% received a tricyclic or MAOI; 36% received anti-anxiety medication; 19%, neuroleptics; 19%, ECT; and 6% received lithium carbonate.

At subsequent 2 and 5 year follow-ups, it was found that between 31% and 50% of patients received no or low levels of antidepressant somatotherapy.^{11,21} Among those who recovered and then relapsed, 47% were found to have received no antidepressant somatotherapy in the 4 weeks before relapse.¹⁰

Likewise, it is not possible to conclude from these data that a causal link exists between low treatment levels and the strong evidence of chronicity and relapse in depressed patients. However, there was a tendency for patients receiving the lowest levels of somatotherapy to remain ill for the longest time.²⁰ This suggests that some severely depressed patients who have been labeled "treatment resistant" may, in fact, have received inadequate levels of treatment and for too short a period.²²

Along with these CDS findings that reflect the undertreatment of depression, several other research groups have published data with the same conclusion. Some researchers have concentrated on whether early intervention will shorten the length of an episode while others have focused on assessing the prospective pattern of recurrence following short-term treatment and recovery. There is concurrence among all the researchers that

prophylactic drug treatment can reduce the risk of recurrence.²³⁻²⁷

Maintenance Treatment for Recurrent Depression

A number of investigators have recently explored the role played by maintenance treatment in the outcome of major depressive disorder. They uniformly note that surprisingly few studies have attempted to address the questions of whether and how early intervention influences the subsequent course of patients' illness, whether somatotherapy shortens episodes and decreases their likelihood, and how the discontinuation of medication affects course.²³⁻²⁵

. . . some severely depressed patients who have been labelled "treatment resistant" may have received inadequate levels of treatment and for too short a period.

Kupfer et al found that it took a median of 25 weeks for patients to achieve stabilization from their initial episode of major depression. Recurrence occurred a median of 40 weeks after the first stabilization.²⁴ The time from second recurrence to second stabilization, however, was 11 weeks, suggesting that patients were stabilized more than twice as quickly the second time. The authors concluded that vigorous, early intervention in the second episode (patients received combined imipramine and interpersonal psychotherapy within 7 days of recurrence) significantly shortened the length of the episode. Interpersonal psychotherapy (IPT) is based on the premise that difficulties in interpersonal relationships are the cause or result of depression, and it focuses on resolution of current conflicts. IPT was developed especially for the treatment of depression. It is a short-term intervention, usually involving 12 to 20 sessions over 12 to 16 weeks. Studies have shown psychotherapeutic techniques, including IPT, to be effective in the treatment of depression and superior to control treatments such as relaxation training or nonscheduled treatment.²⁸

In a recent review of the literature on the treatment of recurrent depression, Thase noted relapse rates of 50% in "recently improved" patients who were switched from somatotherapy to placebo vs a relapse rate of 20% in patients receiving ongoing somatotherapy.²⁵ He also noted that the relapse rate among patients recently terminated from successful short-term cognitive behavioral therapy was 35% vs a rate of 9% in patients who had been in remission for 8 full weeks. He states that "the 8-week period of remission before termination of acute therapy was associated with a strikingly more favorable short-term prognosis."²⁵

Also, according to Thase, studies of maintenance pharmacotherapy suggest that such treatment results in a 30% to 40% reduction in relapses (ie, 50% relapse rates in patients on maintenance treatment, as opposed to 80% relapse rates found among non-maintained patients). However, he says, the costs and benefits of such treatment must be carefully weighed on a case-by-case basis, since long-term somatotherapy entails both economic expense and the risk of side-effects. For patients with short illness cycles, severe symptoms, or inter-episode dysthymia, the benefits of treatment frequently outweigh the costs.²⁵

To discover how early treatment intervention influences the natural course of depressive illness Frank and Kupfer examined the recurrence of depression in the first 18 months following medication withdrawal in 74 recurrent depressives from the same sample discussed above.^{23,25} Forty-five patients with recurrent major depression were followed through two consecutive episodes of illness. All the subjects were participants in a protocol examining the relative efficacy of five different maintenance treatment strategies: 1) the use of interpersonal psychotherapy (IPT-M) alone; 2) IPT-M with active imipramine hydrochloride at the acute treatment dose; 3) IPT-M with placebo; 4) a medication maintenance visit with active imipramine; or 5) a maintenance visit with placebo. Maintenance treatment continued for 3 years, or until a new episode of depression occurred. The investigators found that it took a median of 25 weeks for patients to achieve

stabilization from their initial episode. Recurrence occurred a median of 40 weeks after the first stabilization. The time from second recurrence to second stabilization, however, was 11 weeks, suggesting that patients were stabilized more than twice as quickly the second time.

During the 18-month period, 44 patients experienced a recurrence of illness, 8 dropped out, and 22 remained well. On average, patients received 39.9 weeks of maintenance treatment before recurrence. When factors influencing the time to recurrence were analyzed, only assignment to the IPT-M alone group was found to be significantly related to longer time to relapse. Half of patients receiving medication maintenance visits alone had a recurrence by 21 weeks, while those receiving IPT-M did not reach 50% recurrence until 61 weeks of maintenance. The authors noted that the presence or absence of placebo pills had no effect.^{23,25} Neither age at onset, gender, length of index episode, nor previous number of episodes influenced the time to recurrence.

Interestingly, the patients in the IPT-M-only group attended therapy sessions monthly, making it a relatively simple and low-cost intervention, when compared with the economic costs and possible side effects of long-term maintenance with medication.²³

Contrary to long-held clinical wisdom, patients with major depression experience a significant risk for chronicity, relapse, and recurrence. For patients with "double depression," return to a pre-illness, healthy personality may never be achieved, since the underlying dysthymia frequently persists even after acute episodes of major depression have ended.

Given these facts, and given the high levels of morbidity and mortality associated with depression, it is especially disturbing that this illness is underdiagnosed and undertreated.²¹ It is imperative that clinicians who treat depressed patients remain aware of the perniciousness of the illness and of the many effective options available for its treatment.

Conclusion

Given the complexity of the treatment decision problem, no single re-

port to date fully describes or explains the reason for the gap between the availability of treatments demonstrated by controlled clinical trials to be effective for depression, and the treatment actually received by individual patients in clinical practice. However, the accumulation of concordant findings from different investigators with complementary strengths and weaknesses provides strong evidence that such a gap exists.

There are many issues in the chronicity of depression. When depressive symptoms have abated, continuation therapy should be instituted to keep the disorder in remission and prevent relapse. There are a number of factors that may encumber physician or patient compliance including failure to accurately diagnose, patient refusal or lack of compliance with medications, or clinicians' preference to use strictly psychosocial therapy. There are also concerns about the side effects of antidepressants and about potential for overdosing or misuse.

To address these problems, the National Institute of Mental Health launched the Depression Awareness, Recognition, and Treatment (DART) Program in 1988. This program was designed to alert health care providers and the public to the prevalence and seriousness of depressive disorders and to availability of treatments.²⁹

In This Issue

This issue will focus on the various aspects of depression. It includes an article on bipolar disorder for the non-specialist by Mark Bauer, MD, who uses vignettes to illustrate that although the patients and presentations of this illness may differ, the diagnosis can be made reliably; on depression in medical patients by Richard Goldberg, MD, who explains the prevalence of psychiatric illness in the medical patient population and explores recognition and various methods for evaluation; combined psychosocial and psychopharmacological treatments for depression by Gabor I. Keitner, MD, and Ivan Miller, PhD; on depression and substance abuse by Tim Mueller, MD, Richard Brown, MD, and Patricia R. Recupero, MD, who discuss specific treatment implications; on the neuropsychiatric aspects of depression by

Stephen Salloway, MD, and Jim Duffy, MD, who discuss complex neural mechanisms underlying mood and affect; on personality and depression by M. Tracie Shea, PhD, who provides an overview and discusses future directions for research in this area of depression; and an article by Doug Robbins, MD, who addresses an area of uncertainty in non-psychiatric physicians dealing with depressed children and adolescents. This collection of work represents a strong, comprehensive and diverse approach to better understanding many of the issues involved in depression.

I thank the authors who contributed to this issue of RHODE ISLAND MEDICINE. This collection of work represents the solid, broad variety of interest, expertise and the high quality of work found in the Rhode Island medical community. All contributing authors are on the faculty at Brown University's School of Medicine in the Department of Psychiatry and Human Behavior. The excellence of their manuscripts, their clinical care of patients, their teaching of medical students, and their ongoing research is outstanding. I am also deeply appreciative to Liz Prager for her superb skills as an editorial assistant.

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The Outcomes of Juvenile-Onset Depression

Douglas R. Robbins, MD

Symptoms of depressive disorders in children and adolescents appear not only to represent the disorders with which we are familiar in adults, but they may be associated with particularly persistent or recurrent, incapacitating, and treatment-resistant forms of these disorders.

Our understanding of depression occurring in children and adolescents has undergone a major change in the past two decades. We once regarded symptoms of sadness in the young as manifestations of transient reactions to the vagaries of a young person's experience or as accompaniments of developmental phases, such as the "turmoil" of adolescence.¹ One implication of these ways of thinking was that such symptoms were unrelated to the major affective disorders that were well known in adults and, therefore, that our knowledge about the etiology, genetics, treatment, and outcome of these disorders did not apply. A specific implication was the idea that children and adolescents with such symptoms would "grow out of" them.

A growing body of evidence suggests that this is not the case. Symptoms of depressive disorders in children and adolescents appear not only to represent the disorders with which we are familiar in adults, but they may be associated with particularly persistent or recurrent, incapacitating, and treatment-resistant forms of these disorders. Clarification of these questions is critical both to early intervention with individuals and populations with illnesses associated with very real morbidity and mortality and to our understanding of the etiologies of these illnesses.

Continuity of Juvenile-Onset and Adult Depression

Evidence for the occurrence in childhood and adolescence of the af-

fective disorders known in adults has come first from studies of the phenomenology or pattern of symptom presentation. Empirical studies of child and adolescent psychiatric populations revealed the association of severe, persistent depressed mood with other symptoms of what has been called melancholia, "clinical depression," or currently, major depression.²⁻⁶ In childhood, adolescence, and adulthood, an episode of major depression is defined as a syndrome in which at least five of a group of nine symptoms (Table 1) is present, one of which is depressed mood or diminished interest or loss of pleasure in all, or almost all, activities. A review of three stud-

... there are some indications that earlier onset of affective disorders may be associated with more severe illness.

ies of preschool, elementary school-age, adolescent, and adult psychiatric patients that had used systematic methods of interviewing and comparable diagnostic criteria found a relatively consistent pattern of clustering of the symptoms of depressed mood, insomnia, impaired concentration, suicidal thoughts, across all age groups.⁷ The loss of interest or pleasure in usual activities (anhedonia), the experiencing of worse depression in the morning (diurnal variation), hopelessness, psychomotor retardation, and delusions were associated with increased age, while depressed appearance, low self-esteem, and somatic complaints to be more frequent in depressed children as compared with adolescents, and anhedonia and hopelessness were found to be more common in adolescents. Most strikingly, the occurrence

of suicide attempts, including fatal attempts, increases with the onset of puberty.⁸ Age and development, then, produce variations on the theme of major depression, but the basic phenomenology or symptom pattern is relatively consistent across the life span.

Another point of consistency or continuity is in the familial nature of depressive disorders at all ages of presentation.⁹ Response to treatment—pharmacological or psychosocial—has been inadequately studied in children and adolescents to allow meaningful comparison across age groups.

Thus, we have considerable evidence that the syndrome of major depression in children and adolescents is not a transient reflection of passing circumstances nor an insignificant concomitant of a developmental stage. It appears to be consistent with the disorder we see in adults, which is often recurrent or persistent and associated with serious dysfunction and with suicide.

Studies and Course of Outcome

Studies of the longitudinal course of juvenile-onset depression are few and limited by sample size and methodological considerations. Systematic methods of diagnosis and sequential assessment of symptoms are now available, but they were not in wide use until the last decade. The few studies that have been completed using comparable, systematic methods of assessment, however, suggest that early onset affective disorders are, like those with later onset, associated with serious ongoing morbidity.

One of the first adolescent populations to be studied using systematic diagnostic criteria comparable to those

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used currently was described by Hudgens¹⁰ and followed up after 8 to 10 years by Welner et al.¹¹ Of 16 depressed patients, 1 had committed suicide and 10 of the other 15 had persistent or recurrent depression, most with severe effects on functioning. A longitudinal prospective study of 79 depressed children, mean entry age of 11.2, and 30 non-depressed psychiatrically ill controls found that 72% of those with major depression and 69% of those with dysthymia, a less severe but persistent form, experienced a subsequent episode of major depression within 5 years. In contrast, none of the children with control, non-depressed diagnoses had suffered an episode of major depression.¹² Strober and Carlson followed 60 depressed hospitalized adolescents and found that 80% had at least one recurrent episode of major depression and 20% had an episode of mania.¹³

Thus, evidence is accumulating regarding the recurrent or persistent nature of juvenile-onset depressive disorders. It is premature to compare the frequency of recurrence, times to recovery, or severity of resulting dysfunction to adult disorders, but there are some indications that earlier onset of affective disorders may be associated with more severe illness. Earlier onset appears to be associated with heavier familial loading.⁹ Child and adolescent onset appears to be associated with a high prevalence of other comorbid psychiatric disorders, such as anxiety disorders, conduct disorders, and substance abuse disorders,⁶ all of which are associated with worse prognosis in adults.

The depressed child or adolescent may develop self-destructive ways of temporarily relieving dysphoric mood, such as substance abuse, risk-taking behavior, or premature and impulsive sexual behavior.

Clinicians who treat depressed children and adolescents are concerned that persisting or recurring depression early in life may have particularly deleterious effects. Family relationships

Table 1.—Symptoms of Depressive Disorder in Children and Adolescents

- A. At least five of the following symptoms present in the same 2-week period; one of which is (1) or (2).
 - 1. Depressed or irritable mood, most of the day, nearly every day
 - 2. Diminished interest or pleasure in usual activities
 - 3. Weight loss or gain, change in appetite, or failure to make expected weight gains
 - 4. Insomnia or hypersomnia
 - 5. Psychomotor agitation or retardation
 - 6. Fatigue or loss of energy
 - 7. Feelings of worthlessness or inappropriate guilt
 - 8. Diminished concentration, indecisiveness
 - 9. Thoughts of death, suicidal ideation, or a suicide attempt
- B. 1. Not due to a definable organic factor
 - 2. Not a normal reaction to the death of a loved one
- C. No delusions or hallucinations for as long as 2 weeks in the absence of prominent mood symptoms.
- D. Not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder or other Psychotic Disorders.

Dysthymia

- A. Depressed or irritable mood most of the day, more days than not, for at least 1 year.
- B. Presence, while depressed, of at least two of the following:
 - 1. Poor appetite or over-eating
 - 2. Insomnia or hypersomnia
 - 3. Low energy or fatigue
 - 4. Low self-esteem
 - 5. Diminished concentration or indecisiveness
 - 6. Feelings of hopelessness
- C. During a 1-year period, never without the symptoms in A for more than 2 months.
- D. No evidence of unequivocal Major Depressive Episode during the first year of the disturbance.
- E. No history of Mania or Hypomania.
- F. Not superimposed on a chronic psychotic disorder.
- G. Not due to a definable organic factor.

may be disrupted, interpersonal skills develop aberrantly, academic and vocational skills and skills necessary for basic autonomous functioning may not develop properly. The depressed child or adolescent may develop self-destructive ways of temporarily relieving dysphoric mood, such as substance abuse, risk-taking behavior, or premature and impulsive sexual behavior.

It is also possible that a psychobiological mechanism exists whereby the earlier onset of an affective disorder may play a causal role in a deteriorating course. Post et al¹⁴ have discussed the possible roles of sensitization and kindling in the development of shorter intervals between episodes in patients with bipolar (manic-depressive) disorder, suggesting that the course may not be predetermined but that it may in part be an effect of the severity and frequency of earlier episodes.

Implications

Clearly, the accumulating evidence suggests that we do a disservice to a child or adolescent with major depression to anticipate a benign course or expect him or her to "grow out of it." Further study of diagnostic distinctions is necessary for depression not associated with the full syndromes of major depression or dysthymia (eg, adjustment disorder with depressed mood) may not be associated with subsequent depressive illness. Clarification of the association of diagnostic subtypes or biological parameters with subsequent course (eg, bipolar disorder) is needed.

We are particularly in need of systematic, controlled studies of treatment modalities. The evidence of the severity of these illnesses and the dysfunction and mortality associated with

them suggests the need for aggressive, early, comprehensive treatment, but the efficacy of treatment options in the young is only beginning to be studied in sufficiently large, controlled studies.

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... the accumulating evidence suggests that we do a disservice to a child or adolescent with major depression to anticipate a benign course or expect him or her to "grow out of it."

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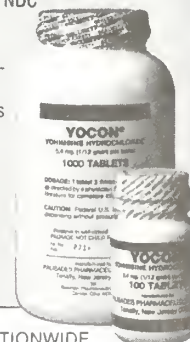
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Depression in Medical Patients

Richard J. Goldberg, MD

Depressive symptoms are a significant problem in medical patients, resulting in impaired physical, social, and role functioning.¹⁻³ While the majority of depressive symptoms represent transient maladaptive reactions to psychosocial stressors, the clinician also must be concerned about the presence of major depression, and depression secondary to some medical factor. This paper will review the prevalence of major depression in medical patients, factors interfering with its recognition, elements of a diagnostic evaluation, and selected issues involving somatic treatment.

Prevalence

The prevalence of major depression in medical patients is significantly higher than the 2.5% found in the community (see Table 1). Unfortunately, the figures reported in Table 1 are complex to interpret because the studies contain many shortcomings involving sample selection and diagnostic methods.⁴ The percentages listed often are not limited to major depression or may reflect lifetime rather than sample prevalence. Overall, from 5% and 20% of the medically ill have significant depression and 2 to 3 times as many patients with depressive symptoms falling short of meeting full diagnostic criteria.⁵⁻⁷

Recognition

Unfortunately, the majority of cases of depression in medical patients are overlooked or inadequately treated, especially in the elderly.⁸⁻¹² Reasons that may account for under-recognition include:

1. Depressed medical patients may present prominent physical rather

than emotional symptoms. Somatization, chronic pain, or functional disability are common presentations that may mislead physicians, especially because such patients often insist they have some medical illness.

2. Depressed medical patients may deny depression. Depression remains stigmatized and is often seen as a sign of weakness. For this reason, it is often helpful for physicians to inquire about "discouragement" as a way of leading into an inquiry about depression.
3. Depressed medical patients, especially the elderly, may be misdiagnosed as demented. Depressed patients often have a significant component of cognitive impairment,¹³ manifesting as indecisiveness or impaired memory. The cognitive impairment of depression is sometimes called "pseudo-dementia," which is important to suspect because, unlike degenerative dementias, it is usually treatable.

The prevalence of significant depression in the medically ill seems to be between 5% and 20%. In addition, there are 2 to 3 times as many patients whose depressive symptoms fall short of meeting full diagnostic criteria.

4. Depression may be ascribed to psychosocial or medical stress and dismissed as a normal behavior. For example, "Wouldn't you be depressed if you had cancer?" is a typical response that usually terminates further consideration of diagnosis or treatment.

Many physicians feel that the identification of a "precipitating event" disqualifies a patient from a diagnosis of major depression. Such thinking may be a residual of an old classification system that dichotomized depres-

Depression remains stigmatized and is often seen as a sign of weakness.

sion into exogenous depression and endogenous depression. Exogenous (or reactive) depression was usually regarded as less serious. In fact, about 50% of major depressions have an identifiable precipitant, and such "precipitated" depressions have the same symptoms, impairment, and medication response as depression without an obvious precipitant.¹⁴

Diagnostic Evaluation

Depressive symptoms in a medical patient should be considered non-specific symptoms that warrant a thorough medical, psychosocial, and psychiatric diagnostic evaluation.

In a depressed medical patient, it is important to consider the following three dimensions, because it may be impossible to sort out which is the "real" cause:

1. Depression secondary to a medical cause.
2. Depression as an adjustment problem.
3. Major depression.

The Medical Evaluation: Many drugs and medical illnesses produce depressive symptoms (Table 2). A common question involves the role of alcohol in producing depressive symptoms. The clinical strategy for such a situation involves a dual-diagnosis approach in which the patient is first de-toxified from alcohol and observed over a period of weeks to see whether the depressive symptoms start to resolve. (For further information on this topic, see the article by Mueller et al in this issue.)

ABBREVIATIONS USED

COPD: Chronic obstructive pulmonary disease
CT: Computerized tomography
ECT: Electroconvulsive therapy
GI: Gastrointestinal
MAO: Monamine oxidase (inhibitors)
SSRI: Selective serotonin re-uptake inhibitor

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Some neurologic disorders involving the central nervous system may lead directly to changes in brain function that create symptoms of major depression¹⁵ (see Salloway and Duffy article in this issue). Strictly speaking, most medical conditions do not cause "major depression" in this way, but may create depressive symptoms (such as fatigue, sleep or appetite impairment) that may be misinterpreted as a primary psychiatric disorder rather than a disorder secondary to the medical condition.

The extent of the search for an underlying medical cause of depression must be matched appropriately to the clinical history and physical examination. It does not make sense to order a comprehensive battery of medical tests on every patient with depressive symptoms. For example, ordering a brain CT scan in an otherwise healthy 35-year-old depressed woman with a normal examination would not make sense. On the other hand, the emergence of depressive symptoms in a 35-year-old woman who had a recent mastectomy should raise considerable suspicion of the possibility of brain metastases because of the high prevalence of brain involvement with that diagnosis.

If a patient has some underlying medical issues that might be responsible for the depressive symptoms, these potential causes should, if possible, be corrected and the patient should then be re-evaluated.

The Psychosocial Evaluation: It is important not to overlook the potential psychosocial dimensions of the depressed patient. Ideally, one could simply ask the patient "Why do you think you are feeling depressed?" The patient could then be given appropriate psychotherapy to address the cause. Unfortunately, patients may not be able to articulate a clear issue because of denial, resistance, or lack of full awareness of the connections involved.

The physician can best make this assessment by systematically reviewing the major psychosocial domains of experience. Goldberg and Novack¹⁶ have described the "psychosocial review of systems" that can be used to guide a comprehensive overview of these areas. A semi-structured interview is often necessary because patients consistently under-report per-

Table 1.—Prevalence of Depression in Selected Medical Patients

Alzheimer's Disease	15-55% ^{63,64}
Cancer Patients	
Inpatients	42% ⁶⁵
Gastrointestinal	20% ⁶⁶
Gynecologic	23% ⁶⁷
Coronary Artery Disease	18-26% ⁶⁸
Cushing's Syndrome	67% ⁶⁹
Diabetes Mellitus	33% ⁷⁰
End Stage Renal Disease	30% ⁷¹
Epilepsy	55% ⁷²
HIV Positives	7-15% ⁷³
Huntington's Disease	32-41% ⁷⁴
Multi-Infarct Dementia	27-60% ⁷⁵
Multiple Sclerosis	6-57% ⁷⁶
Myocardial Infarction	18% ⁷⁷
Pain (Chronic)	32% ⁷⁸
Parkinson's Disease	40% ⁷⁹
Renal Dialysis	8% ⁸⁰
Stroke	30-50% ⁸¹

sonal distress to their physicians.¹⁷

There are times when patients are not psychologically minded or are so symptomatic that they are unable to participate in or benefit from a psychotherapy approach. In those cases, the psychosocial dimension is best re-evaluated after other somatic treatments have had a chance to reduce symptoms.

The Psychiatric Evaluation: After considering the potential medical and psychosocial dimensions, the clinician needs to consider some additional diagnostic issues before deciding that the patient has major depression. While a complete differential diagnosis is beyond the scope of this article, it is important to inquire about the possibility of bipolar illness, psychotic symptoms, anxiety disorders, and chronic personality difficulties¹⁸ (also see Shea article in this issue).

The Use of Anti-Depressants in Medical Patients

When the potential medical causes of depression have been identified and corrected (insofar as it is possible to do so), and the psychosocial stresses have addressed (when it is possible to do so), then the decision to use anti-depressants is based on the presence of target symptoms. That is, if the patient has significant sleep and appetite dis-

turbance, fatigue, depressed mood, and anhedonia, then anti-depressants may be used appropriately as a component of the treatment. This approach is known as the "target symptom approach" but does not imply a lack of differential diagnostic thinking.

Once a decision is made to use anti-depressants in a medical patient, there are a number of special considerations relating to side-effects that must be kept in mind. Table 3 summarizes the current anti-depressants available and their relevant side effects. This table does not include MAO inhibitors or stimulants,^{19,20} which are best reserved for use by specialists. This article also does not review other drug groups that have demonstrated anti-depressant activity such as the triazolo benzodiazepines (eg, alprazolam)²¹ and the azapirones (eg, buspirone).²²

The choice of an anti-depressant is generally made on the basis of side effect profile, since there are no significant efficacy advantages among the choices.

This section is not intended to be a comprehensive review of the pharmacology of the current use of antidepressants,²³ but a review of selected side effect issues pertinent to medical patients. Descriptions of other side effects issues including rash,²⁴ sexual dysfunction,^{25,26} and seizures²⁷ are available. Management of some of these side effects has also been reviewed.²⁸

1. Anti-cholinergic activity: It is generally a good idea to minimize anti-cholinergic burden. It can cause "nuisance" side effects such as blurred vision, dry mouth, and constipation. However, these side effects can become extremely serious. Patients with GI pathology (or decreased motility from other medications such as narcotics) may develop paralytic ileus. Men with prostatic enlargement or patients with autonomic dysfunction can develop urinary retention. Mydriasis and cycloplegia may precipitate narrow angle glaucoma.²⁹ Cancer patients may develop stomatitis and elderly patients have a high potential for confusion.

Anti-cholinergic toxicity is a greater risk when multiple drugs with anti-cholinergic activity are used, such as diphenhydramine (Benadryl), thioridazine (Mellaril), benztrapine (Co-

Table 2.—Selected Medical Conditions and Drugs⁸² Associated with Depressive Symptoms

Medical Conditions	Drugs
Brain Tumor	Alcohol
Cancer	Alpha-Methyldopa
Coronary Artery Disease	Amantadine
Dementia	Anabolic Steroids
Diabetes Mellitus	Anti-Cholinergics
Epilepsy	Anti-Convulsants
HIV Positivity	Barbiturates
Hypercalcemia	Benzodiazepines
Hypercortisolism	Cimetidine
Hypokalemia	Clonidine
Hypothyroidism	Corticosteroids
Hypoxia	Methyldopa
Liver Failure	Oral Contraceptives
Multiple Sclerosis	Propranolol
Parkinson's Disease	Ranitidine
Renal Failure	Reserpine
Sleep Apnea	Sedatives
Stroke	Stimulant (Withdrawal)
	Thiazides

gentin), or meperidine (Demerol). Nursing home patients and surgical patients may have significant confusion that is due to cumulative anticholinergic burden.^{30, 31}

2. Sedative or activating effects:

The sedating properties of these medications often are a consequence of central histamine receptor blockade, although some of the agents (such as trazodone) probably cause sedation through effects on serotonin. Generally, the anergic, withdrawn, hypersomnic patient better tolerates a stimulating agent, while the agitated, anxious, insomnic patient may better tolerate a sedating agent.

Activation side effects may help the patient feel less fatigued; however, problems of activation may take the form of tremor, restlessness, and insomnia. A small percentage of patients experience a dysphoric hyperarousal when given anti-depressants.³² The selective serotonin re-uptake inhibitors (SSRIs) may cause either sedation or activation.³³

3. Hypotensive effects: Orthostatic hypotension is a frequent side effect of anti-depressants^{34,35} that occurs from blockade of peripheral alpha adrenergic receptors and from a central brain stem mechanism. Four percent of elderly patients started on imipramine fall and sustain an injury.^{36,37} It is important (for patients on tricyclics) to measure orthostatic readings

before and during treatment, especially for older patients, those at prolonged bed rest, and those who are volume-depleted due to poor intake. Many of the second generation antidepressants do not have this side effect, as indicated by a "0" in Table 3.³⁸

4. Gastrointestinal (GI) effects:

The tricyclic anti-depressants may cause some GI side effects as a result of constipation or relaxation of the gastro-esophageal sphincter resulting in some increased gastric reflux. The anti-depressants known as the SSRIs have GI side effects as a common problem, specifically nausea (about 15%) and diarrhea.^{39,40} The anorexic effects can also be a problem for some patients; however, when loss of appetite is a symptom of major depression, successful treatment of the depression with the medication often has the effect of curing rather than worsening the eating problem.

5. Cardiac effects: The cardiac effects of the anti-depressants have been repeatedly reviewed.⁴¹ The tricyclic antidepressants are known to delay cardiac conduction in the intraventricular portion of the His bundle.⁴² Therefore, patients over age 40, or those with a history of cardiac disease, should have a screening electrocardiogram before starting on a tricyclic to make sure there is no conduction delay. Patients with isolated right bundle branch blocks or left anterior

hemi-blocks are usually safe to have on tricyclics, although if there is any doubt it is probably wise to consider a second generation anti-depressant.

Tricyclic anti-depressants also have quinidine-like effects, in the Class 1A anti-arrhythmic category.⁴³ Therefore, if a patient has cardiac dysrhythmias, it is important to consider if quinidine would be contraindicated. If so, the tricyclics are also contraindicated.

At therapeutic doses, tricyclics are not myocardial depressants. However, they are extremely dangerous in overdose and remain the prime cause of overdose deaths in the United States, requiring careful monitoring.⁴⁴

The second generation antidepressants appear to have fewer cardiac problems than the tricyclics, though there are small, steady numbers of cardiac side effect case reports.⁴⁵⁻⁴⁸

6. Seizure potential: All the anti-depressants, except for paroxetine, lower seizure threshold. The rate of seizure induction for the tricyclics is about 1 per 1000 and is 4 times higher, 4 per 1000, for bupropion.⁴⁹ This potential is not a reason to avoid using antidepressants in seizure patients, as long as their seizures are controlled on anti-convulsants. New-onset seizures in someone started on an anti-depressant warrants a work-up.

7. Dosing and Interactions: Table 2 lists the plasma elimination half-lives and dose parameters of the anti-depressants. Note that many of the tricyclics have a half-life of about 1 day. Hence, many of them can be prescribed on a once per day basis. Fluoxetine (or more accurately, its active metabolite) has a half-life of about 7 days. Therefore, this drug takes 3 to 4 weeks to reach a steady state and will take as long a time to be eliminated if it is discontinued. This long half-life is also the reason that some of the side effects associated with fluoxetine may not appear for several weeks.

The column labeled "Dose Range" indicates the usual oral dose range that is necessary to achieve a therapeutic response. The numbers "100-300" would mean an oral dose of 100 to 300 mg per day would be reasonable. Some of the anti-depressants have research data that have established a therapeutic plasma level. For example, nortriptyline has a therapeutic "window" such that a plasma level between 50 and

Table 3.—Anti-Depressant Summary

	Anticholinergic	Sedation	Activation	Hypotension	His ² Bundle	G.I. Activation	Seizures	Half-life (hour)	Dose Range	Tx Level ng/ml
Amitriptyline ¹ (Elavil)	4	3	0	3	+	0	+	20-46	100-300	75-175
Clomipramine ¹ (Anafranil)	4	2	0	3	+	0	+	20-40	50-250	
Nortriptyline ¹ (Pamelor)	2	2	0	1	+	0	+	18-88	50-150	50-150
Imipramine ¹ (Tofranil)	3	2	1	3	+	0	+	4-34	100-300	>265
Desipramine ¹ (Norpramin)	2	1-2	2	2	+	0	+	10-32	100-300	100-160
Doxepin ¹ (Sinequan)	3	4	0	2	+	0	+	8-47	100-300	
Protriptyline ¹ (Vivactil)	4	1	3	2	+	0	+	53-124	10-60	
Trimipramine ¹ (Surmontil)	3	3	0	3	+	0	+	9	100-300	
Amoxapine (Ascendin)	2	2	1	1	?+	0	+	8	100-600	
Bupropion (Wellbutrin)	1	0	3	0	0	0	++ ++	8-24	150-300	
Fluoxetine (Prozac)	0	1-2	1-2	0	0	1-2	+	7 Day	20-60	
Maprotilene (Ludiomil)	2	3	1	1	+	0	++	27-58	100-300	
Paroxetine (Paxil)	1	0-1	1-2	0	0	1-2	0	24	10-50	
Sertraline (Zoloft)	0	1-2	1-2	0	0	1-2	+	26	50-200	
Trazodone (Desyrel)	0	3	0	2	0	0	+	6-14	100-600	

1 The first eight anti-depressants are "tricyclics"

2 His bundle "+" indicates delayed conduction

150 ng/ml is considered effective. Elderly and medically ill patients generally should be started on the lower end of the dose curve to be sure they can tolerate the medication, and then gradually raised to a usual therapeutic level.

Drug interaction with medical patients also should be considered. The tricyclics, because of their side effect profile, augment drugs that have similar side effects. For example, patients on diphenhydramine (Benadryl), which has anti-cholinergic activity, will be more likely to develop an anti-cholinergic syndrome; patients on nitrates for ischemic heart disease will be more likely to develop hypotension; and patients on quinidine will have that property augmented. The SSRI group is notable for its effects on the cytochrome P-450 enzyme system involved in the metabolism of many other drugs. Therefore, there is a significant possibility of a clinically im-

portant drug interaction for patients on one of these anti-depressants. Among the SSRIs, fluoxetine has the most potent effects, often resulting in raising the plasma level of a co-prescribed drug by 3 to 4 times. Paroxetine has some clinically relevant effects in this area, but much less than fluoxetine. Sertraline is the least likely to cause any clinically relevant augmentation of other drug levels. Because there are so many possible interactions, the clinician should inquire with a drug information source when in doubt.

Use of ECT in Medical Patients:

ECT remains an important and effective intervention in depressed medical patients. Most of the public and many physicians continue to underestimate the safety and efficacy of this procedure. The indications for ECT⁵⁰ are: 1) failure to respond to two good

clinical trials of antidepressants; 2) inability to tolerate antidepressants because of side effects; or 3) need for a rapid response due to potentially life-threatening symptoms.

There are virtually no absolute contraindications to ECT. In fact, ECT has been successfully performed in patients with many severe medical conditions, including those with implanted electrical cardiac defibrillators.⁵¹ Patients with space-occupying intracranial lesions with elevated intracerebral pressure should not be given ECT. Patients with unstable orthopedic conditions should be treated cautiously because of the potential for some muscle traction during the procedure, even though succinylcholine abolishes significant muscle activity in the seizure.

The final problem area for ECT in medical patients involves the ability to tolerate anesthesia. Patients are given a short-acting intravenous barbiturate

and then have respiration assisted by hand ventilation with supplementary oxygen. Patients with severe COPD are sometimes considered too high a risk for such a procedure. When in doubt, anesthesia consultation is in order before considering ECT. A comprehensive review of ECT in the medically ill is available.⁵²

Summary and Conclusion

Depression is a major problem in medical patients. It is a problem that has been generally under-recognized and under-treated, highly associated with somatized symptoms, loss of function, and increased medical utilization.^{53,54} Obviously more training needs to be provided in this area for non-psychiatric physicians, as well as other primary care providers.

The choice of an antidepressant is generally made on the basis of side-effect profile, since there are no significant efficacy advantages among the choices.

Much of what guides recognition and treatment of depression in medical patients has been derived from studies of depression in non-medical populations. However, it is not completely clear that depression in medical populations is the same problem as that seen in the mental health care setting. Furthermore, the majority of psychopharmacology studies have been done in patients with no medical conditions. There are, fortunately, increasing numbers of drug and ECT studies in specific medical populations⁵⁵⁻⁵⁹ as well as outcome studies in medically ill depressed patients.^{60,61} There has been increasing recognition that in the primary care setting, less severe depressive symptom constellations are a common problem. This so-called "sub-syndromal" depression is an area of great interest but little understanding. There is no well researched information on such depressions in terms of natural course, response to treatment, or relation to other disorders such as anxiety disorders.

It is hoped that non-psychiatric physicians will increasingly recognize

depression in their patients and feel comfortable in its evaluation and initial management. Clinical practice guidelines, which may be helpful to primary care physicians, are currently being developed.⁶² When patients seem difficult to manage or diagnose, consultation should be sought from psychiatrists familiar with the special presentations and problems of working with this population.

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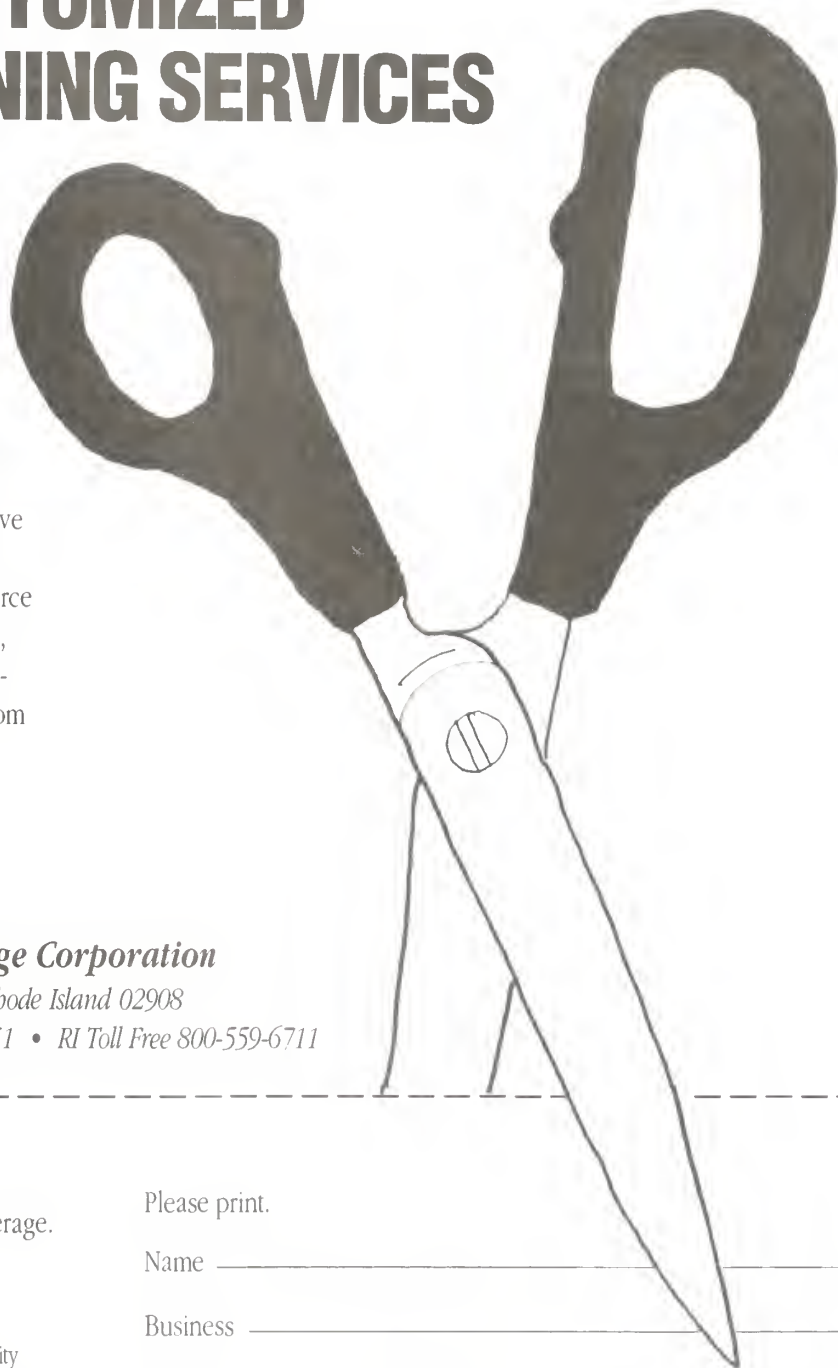
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Bipolar Disorder for the Non-Specialist: Clinical Features, Morbidity, and Management Strategies

Mark S. Bauer, MD

Bipolar disorder is defined as a recurrent, major mood disorder characterized by episodes of major depression plus episodes of mania or hypomania, a milder form of mania.

Dr A was a 35-year-old male in surgical subspecialty training. Although generally outgoing and friendly, he had become withdrawn and quieter than usual with colleagues for several months. Subsequently, he began to work more energetically and incessantly, becoming more pushy and irritable than usual, but also inappropriately jocular and informal with colleagues and staff at various times. He frequently arrived at work disheveled, with stories about how he had been out all night, sometimes for several nights in a row. He appeared to have spent substantial amounts of money on car and clothes and spoke extensively about what appeared to be several high-risk business ventures he had become involved in with unsavory characters. He was soon dismissed from his training program for presumptive drug use.

Ms B was a 42-year-old who held a high-level managerial position in a large concern. Although she was known for her creativity and drive and had been highly successful in all her administrative endeavors, periodic absences, difficulties meeting deadlines, and apparent moodiness kept her from advancing to the highest levels in her field. Only her husband and her physician knew of her three suicide attempts in recent years.

Mr C was a 55-year-old chronically unemployed single male whose sole source of income was a veteran's medical pension plus Social Security disability payments for his chronic psychiatric illness. He had been maintained for several years on lithium carbonate and occasional other psychotropic medications. He lived indepen-

dently and managed his medical and mental health needs appropriately, although he had a limited social life and had not sought work for several years. On his most recent presentation to the clinic he was irritable and caustic with the staff, and was convinced that his computerized laboratory results were part of a large government database on him, which he believed to be related to his work with the CIA while in the service. He rejected medication adjustments as further attempts by the government to control him and left the clinic.

Each of these case vignettes describes a person with bipolar affective disorder, formerly known as manic-depressive illness. As is clear from the vignettes, each case involves substantial morbidity. Each is true.

While the presentation of bipolar disorder can be variable, and while the persons affected may be quite different in personality and life history, the diagnosis of bipolar disorder can be reliably made by appropriately trained clinicians. Most importantly, once recognized the disorder can be successfully treated. This review will briefly summarize the clinical features of bipolar disorder, its morbidity, current treatment strategies, and hypotheses regarding mechanism.

Clinical Features of Bipolar Disorder

Bipolar disorder is classified as a mood, or affective, disorder in the International Classification of Diseases (ICD) and the *DSM* classification system,¹ soon to be codified in its fourth revision, *DSM-IV*. Other mood disorders include major depressive disorder, dysthymia, and cyclothymia. Mood disorders are best conceptualized in terms of episodes and disorders. *Episodes* denote distinct periods

of altered function. The number and type of episodes determine the *disorder*, as summarized in Table 1. Bipolar disorder is defined as a recurrent major mood disorder characterized by episodes of major depression plus episodes of mania or hypomania, a milder form of mania. *Major depressive episodes* are defined by discrete periods of depressed or blue mood or loss of interest or pleasure in life that endure over weeks. These symptoms are frequently accompanied by changes in sleep, appetite, energy, cognition, and judgment, among other symptoms. Depressive episodes in major depressive disorder are indistinguishable from those in bipolar disorder; the differential diagnosis is resolved by longitudinal course rather than cross-sectional symptom profile.

Manic episodes are defined by discrete periods of abnormally elevated, expansive, or irritable mood accompanied by marked impairment in judgment and social and occupational functioning. These symptoms are frequently accompanied by unrealistic grandiosity, excess energy, and increases in goal-directed activity that frequently have a high potential for painful consequences. Classically, mania has been considered to be the opposite of depression in terms of mood: manics are often cheery, optimistic, and self-confident. However, during a manic epi-

ABBREVIATIONS USED

AMP: Adenosine monophosphate
DSM: Diagnostic and Statistical Manual
ECA: Epidemiologic catchment area
ECT: Electroconvulsive therapy
EEG: Electroencephalogram
FDA: Food & Drug Administration
NIMH: National Institute of Mental Health

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sode a person may also be subjectively uncomfortable, or irritable in mood. The core symptoms of the syndrome appear to be symptoms of increased drive to be active, increased energy, and increased speed of thoughts, rather than primarily mood-related symptoms.² Whether euphoric or dysphoric, manic episodes often can lead to dangerous social situations, including spending sprees, adverse sexual encounters, and social or business commitments that lead to interpersonal or legal difficulties. *Hypomania* is by definition milder than mania. Bipolar disorder with hypomania is sometimes called *Bipolar type II*, in contrast to *Bipolar type I*, which is the category for anyone who has experienced a manic episode.

Up to 15% of persons with type I or type II disorder may experience frequent, sometimes temporally linked, episodes; this pattern is known as rapid cycling, formally defined as four or more mood episodes in 12 months.^{27,28} Concurrent mania and depression, known as a *mixed episode*, is also not infrequent during bipolar disorder.

Hypomania may sometimes be adaptive. In fact, "psychohistories" of several famous persons have attributed their high energy, creativity, and self-confidence to hypomania. While this may be apparent in some persons with bipolar disorder seen in typical clinical practices, to call bipolar disorder the "genius disease," as was recently done in a popular magazine, is to trivialize the very real suffering experienced by persons with the disorder—including the famous. *Dysthymia* and *cyclothymia* are the "minor" mood disorders, the former characterized by chronic depressive symptoms and the latter by chronic bipolar mood swings. In both disorders the severity of symptoms is by definition less than for the corresponding major mood disorders. Much less is known about cyclothymia than about the other mood disorders since the boundaries with normal mood variability are less distinct. Also, cyclothymics are typically less consistently troubled by their symptoms and therefore present for mental health treatment less frequently than persons with other mood disorders. However, it is likely that persons with cyclothymia are commonly seen in medical settings for

Table 1.—Summary of Mood Episodes and Mood Disorders

Episode	Disorder
Major Depressive Episode	= Major Depressive Disorder, Single Episode
Major Depressive Episode + Major Depressive Episode	= Major Depressive Disorder, Recurrent
Major Depressive Episode + Manic Episode	= Bipolar Disorder, Type I
Major Depressive Episode + Hypomanic Episode	= Bipolar Disorder, Type II
Chronic Subsyndromal Depression	= Dysthymia
Chronic Fluctuations between Subsyndromal Depression and Hypomania	= Cyclothymia

health care for other problems. It is also probable, because of instability in their mood and consequently their social and occupational performance, that persons with cyclothymia are frequently misdiagnosed by both mental health and other medical caregivers as having personality disorders.

Bipolar disorder is common, with a lifetime prevalence of nearly 1%.³ There is an even gender distribution for bipolar disorder, in contrast to the female preponderance in major depressive disorder. Bipolar disorder tends to run in families, with 5% to 15% of relatives of bipolar probands affected with the illness; rates of major depressive disorder are also high in families of persons with bipolar disorder, ranging from 5% to 25% compared to 5% to 6% for normal subjects. Rates of comorbid alcohol and drug abuse are among the highest for any psychiatric disorder, ranging from 15% to 60% compared to 2% to 25% for major depressive disorder.⁴

Table 2.—Consider the Diagnosis of Bipolar Disorder If:

- Multiple bouts of depressive symptoms
- Post-partum depression or psychosis
- Significant mood swings across the menstrual cycle
- Episodic "personality changes" (hypomania? substance use?)
- Delusions or hallucinations in a previously well-adjusted person
- History of bouts of depressive symptoms and drug or alcohol abuse (not necessarily at the same time)

Bipolar disorder may be more common in the upper socioeconomic classes, for reasons that are not yet clear. Several theories have been advanced to explain this "upward drift," including the adaptive aspects of milder forms of the disorder in families of persons with the disorder or in the person him/herself. While there is some evidence for a tendency to under-diagnose bipolar disorder and to over-diagnose more severe disorders such as schizophrenia in the lower socioeconomic classes, this artifact alone cannot explain the upward drift of bipolar disorder.

The typical age of onset for bipolar disorder is mid-20s, with a second peak of onset in the mid-40s for women. The post-partum period may be a time of particular vulnerability for persons with bipolar disorder, both for depressive and psychotic episodes. Mood episodes are occasionally menstrually linked; although this is the exception rather than the rule, bipolar type II disorder is occasionally misdiagnosed as premenstrual syndrome.

Persons with bipolar disorder average seven to nine episodes over the course of a lifetime. In persons with a rapid cycling pattern, occurrence of up to 50 episodes over the course of the illness is not uncommon. It was classically thought that bipolar disorder follows an episodic course, characterized by discrete onset and offset of affective episodes with return to pre-morbid baseline between episodes; this view has its roots in the observation by Kraepelin that an episodic course distinguished bipolar disorder from schizophrenia, which had a steadily deteriorating course.⁵ How-

ever, more recent evidence indicates that substantial pathology may remain in terms of chronicity of index episode, interepisode subsyndromal symptoms, and decrements in social and occupational function. For instance, 7% to 32% of persons with bipolar disorder may remain in a major affective episode after 18 months.⁶ Although less well studied, subsyndromal affective symptoms may remain in 13% to 34%, despite adequate treatment.⁷

Morbidity of Bipolar Disorder

Substantial functional (ie, social and occupational) impairment accompanies even subsyndromal depression, as has been amply demonstrated in the Medical Outcome Study,⁸ the Epidemiologic Catchment Area (ECA) Study,⁹ and in formal research studies of major depressive disorder. Not surprisingly, substantial levels of functional impairment are also characteristic of bipolar disorder. For example, 19% of persons with bipolar disorder will attempt suicide at some time in their lives.¹⁰ Without adequate treatment a person with bipolar disorder can expect from age 25 to lose 14 years of effective major activity (eg, work, school, family role function) and 9 years of life.¹¹ Divorce rates for persons with bipolar disorder are significantly higher than for normals or persons with major depressive disorder.^{12,13}

Persons with bipolar disorder may be left disabled even when major disease-specific indices have improved.¹⁴ For example, Dion et al¹⁵ found that although 80% of their sample of persons with bipolar disorder became symptom-free by 6 months after an index major affective episode, only 43% were employed, and only 21% were employed at pre-episode levels. Harrow et al¹⁶ found at 1.7 years of prospective follow-up after an index manic episode 23% of the sample was continuously unemployed, with 36% underemployed compared to pre-episode levels. Five-year follow-up data from the NIMH Collaborative Program on the Psychobiology of Depression found impaired work, social, marital, and recreational function in 30% to 50% of persons with bipolar disorder. Over 55% had fair to poor

Table 3.—Complexities in the Assessment and Management of Bipolar Disorder

- Differential diagnosis can be difficult:
 - Mania may be confused with schizophrenia
 - Hypomania may be overlooked or ascribed to personality disorder
 - Depression, mania, or hypomania may be misunderstood as a primary alcohol or drug problem
- The morbidity and mortality of under-treated bipolar disorder is substantial***
- High rates of comorbidity with alcohol or drug abuse require specialty assessment and management
- Management requires a combination of medication and psychoeducation/psychotherapy
- Minimization of medication side effects is essential to compliance and illness acceptance
- Optimization of medication dosing and combination treatment requires careful monitoring

*** All persons with suspected bipolar disorder should be assessed for current and prior suicidality as part of the routine history and mental status examination!

sense of satisfaction or contentment with their lives and fair to poor overall social adjustment.¹⁷ It is not clear whether such impairment is due to incompletely resolved major affective episodes, medication side effects, demoralization due to the life disruption of having a chronic illness, or a combination of the three, and each has markedly different treatment implications.

In dollar terms, the direct treatment costs of bipolar disorder are substantial. Among the major mental disorders the rate of hospitalization for bipolar disorder is exceeded only by that for schizophrenia.¹⁰ The indirect costs of this disorder are also substantial, since 15% are unemployed for at least 5 consecutive years, while more than 25% of persons under age 65 with bipolar disorder receive disability payments.¹⁰ Such indirect costs, including lost productivity, necessary social system supports, and related costs, accounted for 55% of the costs of non-addictive mental illness in the United States in 1986,¹⁸ compared to 39% in 1955.¹⁹ The societal costs for disability due to mood disorders in particular may be even higher, accounting for as much as 75% of the costs of affective illness.²⁰ It stands to reason, therefore, that treatments targeted at reducing functional impairment will be as necessary as treatments aimed at symptom reduction if the disorder is truly to be eradicated.

Treatment for Bipolar Disorder

Before the 1960s bipolar disorder was managed with treatment targeted only towards resolution of individual episodes. Antidepressants and electroconvulsive therapy (ECT) were used for depressive episodes, and neuroleptics and occasionally ECT for mania.

The advent of lithium treatment revolutionized care for bipolar disorder. Lithium not only provided an additional treatment for acute mania and depression in bipolar disorder, but also was demonstrated to have substantial prophylactic effects on both manic and depressive episodes.⁴ Lithium clearly reduced the direct and indirect dollar costs of bipolar disorder compared to pre-lithium treatment modalities.²¹

The principles of lithium management are fairly straightforward. Serum levels must be kept within the therapeutic range, with renal and thyroid function monitored regularly as well. Breakthrough depressive and manic episodes are usually treated by adding antidepressants or antimanic medications to lithium.

Although not yet FDA-approved for treatment of bipolar disorder, the anticonvulsants carbamazepine and valproic acid may be effective in the treatment of mania^{22,23} and in the prophylaxis of depressive and manic

episodes.^{24,25} These properties are not shared by other anticonvulsants, such as dilantin or clonazepam. Interestingly, response to mood-stabilizing effects of carbamazepine and valproate appears to be independent of any neurologic or electroencephalographic abnormalities. Clearly these agents represent important new tools in the treatment armamentarium for bipolar disorder, and may hold clues to its underlying neural mechanisms.

However, pharmacotherapy for treatment of acute episodes and effective prophylaxis is more complex than simply monitoring lithium or anticonvulsant levels. Approximately 20% to 40% of persons with bipolar disorder do not respond to lithium,²⁶ and the figure may increase to as much as 80% for certain subgroups such as those who experience a rapid cycling pattern or mixed manic and depressive episodes.⁶ There may also be substantial iatrogenic morbidity associated with the pharmacologic treatment of bipolar disorder. For example, antidepressants may worsen the course of bipolar disorder by precipitating mania, mixed states²⁹ or rapid cycling.³⁰

Medication side effects lead to discontinuation of treatment in 18% to 53% of persons with bipolar disorder, a proportion that is higher in lower socioeconomic classes.⁴ Lithium has been the most intensively studied of such treatments, and it appears that its discontinuation may be due to side effects that are easily recognizable in the medical model, such as tremors, weight gain, increased thirst and urination, or gastrointestinal upset. However, equally problematic are the complaints that are usually hesitantly offered only after the person has established a trusting relationship with the caregiver: "I feel controlled" or "Lithium takes away my zest for life." These complaints may represent a sense of emotional blunting and fatigue that sometimes accompanies lithium treatment.

Paradoxically, however, adverse response to effective treatment of the disorder may also be due to the disruption that resolution of symptoms may cause in the lives of affected persons, however impaired they may have been. For instance, persons who have depended heavily for occupational achievement or social functioning on

the energy and self-confidence that often accompanies mania or hypomania, may find it difficult to readjust to "merely mortal" function—particularly if there are also medication side effects that can damage self-esteem, such as weight gain or worsening of acne. Frequently these concerns are not brought up to the treating clinician directly but are expressed in noncompliance, or even termination of treatment. Thus coordinated treatment systems where medication management is supplemented by psychoeducation, and, if necessary, psychotherapeutic interventions for the individual and his/her family are most likely to be successful in eradicating the morbidity associated with bipolar disorder. Medications given in isolation are unlikely to be the panacea for bipolar disorder.

Pathogenic Mechanisms of Bipolar Disorder

As with most psychiatric illnesses, the mechanisms that underlie bipolar disorder are not well understood. Interestingly, most of what we know comes from deductions about successful treatment strategies, rather than the more typical situation for biomedical illnesses in which a pathogenic mechanism is discovered and treatments developed subsequently. Depression itself can be considered a multi-system disease, involving, for example, sleep, appetite, sexual function, and cognition—all of which improve with appropriate treatment using agents that are active on neural catecholamine or serotonin systems. Depressive episodes in bipolar disorder can be considered similarly, although one fascinating aspect of antidepressant treatment of bipolar disorder is that these agents can quite quickly "switch" some persons from depression into mania or hypomania. Thus it is likely that some discrete, probably simple, mechanism is responsible for the varied behavioral pathology in bipolar disorder.

As noted above, lithium is an effective acute and preventive treatment for both depressive and manic or hypomanic episodes. Its therapeutic effects are not shared by other monovalent cations, and it does not appear to be effective in other psychiatric illnesses such as schizophrenia. Approx-

imately 1000 papers per year are published on this simple element in relation to psychiatric illness, yet its mechanism of action remains obscure. After administration, lithium is distributed widely throughout the brain and is handled similarly to the sodium ion in many cellular systems. Effects on catecholaminergic, serotonergic, and cholinergic systems have been described. Currently, one of the more attractive hypotheses is that lithium may exert its therapeutic effect via alterations of the phosphatidylinositol "second messenger" system, which, like the cyclic AMP system, is a key step in signal transduction in the post-synaptic cell.³¹

The utility of the anticonvulsants that are used successfully in temporal lobe epilepsy surprisingly has not focused attention on that brain area, although, as noted above, frank EEG abnormalities are not required for clinical response. Carbamazepine, which has been the most extensively studied of the mood-stabilizing anticonvulsants, has a tricyclic structure as do many antidepressants and neuroleptics; however, it lacks the typical effects of those drugs on catecholamine or serotonin action. One potentially useful heuristic model for bipolar disorder is based on anticonvulsant effectiveness: In animals, delivering subconvulsant stimuli to particular brain areas can lead to spontaneous seizures; such "kindling" can be prevented by treatment with carbamazepine. By analogy, it has been suggested that bipolar disorder may develop because stress-based mood responses to environmental stimuli eventually lead to an autonomous course of mood symptoms.³²

Environmental factors may also be relevant to understanding the mechanisms that underlie bipolar disorder. Twin and adoption studies indicate that there is clearly a genetic, or at least congenital, component to the illness;³³ however, a substantial amount of the penetrance in expression remains to be explained, and a portion is undoubtedly environmental. Although the post-natal events that lead to the onset of the disorder, both physiologic and environmental, have not been identified, individual episodes during bipolar disorder may be associated with psychosocial stressors (including positive ones). However, most episodes

in bipolar disorder are not stress-associated.

Physical environmental factors may also be associated with episode onset. For instance, there is a prominent seasonal pattern to the occurrence of mania, with spring and fall being the most vulnerable periods.⁴ There is also preliminary data that light treatment for seasonal affective disorder may precipitate manic symptoms in susceptible individuals,³⁴ suggesting that ambient light exposure may be involved.

Thus it is likely that a complete understanding of the mechanisms of bipolar disorder will include molecular biological, pharmacologic, neuroanatomic, and environmental components. Both psychosocial and physical environmental factors are likely to have important impacts on the course of the disease.

Encountering Bipolar Disorder in the Non-Psychiatric Medical Setting

Since bipolar disorder has a prevalence of approximately 1%, it is likely that all medical caregivers will encounter at least several persons with the illness, recognized or unrecognized, during their work. The illness is likely to affect the treatment of such persons for reasons that range from medication interactions to behavioral pathology including comorbid substance abuse. As with any other biomedical illness, the first step to appropriate management is accurate diagnosis. And the first step to accurate diagnosis is considering the disorder first.

As summarized in Table 2, signs that bipolar disorder should be considered as a diagnosis include depressive symptoms, particularly multiple bouts; post-partum depression or psychosis; extreme menstrually related mood swings; episodic "personality changes," such as variable energy, drive, pattern of social interactions, and judgment; and the new onset of psychotic symptoms, such as delusions and hallucinations, in a previously well adjusted person. If a person has a history of both substance abuse and depression they should be questioned carefully for a history of manic symptoms as well, which would make the diag-

nosis of bipolar disorder (Table 1).

After screening history, referral for a psychiatric evaluation is the next step (Table 3). This is because the differential diagnosis can be difficult when depression is accompanied by either the milder or most severe forms of mania. Further, the morbidity and potential for mortality with the disorder is high, and management using both medication and psychoeducation/psychotherapeutic tools is probably most likely to be successful. All persons with suspected bipolar disorder, no matter how mild, should be screened for current and past suicidality as part of the routine history and mental status examination.

The high comorbidity with drug and alcohol abuse and dependence complicates management substantially and necessitates consultation with someone with expertise in treating the addictions. Management of medication side effects can be tricky and counterintuitive (eg, certain diuretics can be used to decrease lithium-induced polyuria), and can sometimes make the difference between acceptance and denial of illness. Finally, management with multiple medications is often necessary, at least for limited periods of time. Optimal titration of lithium, anticonvulsants, and the other episode-specific medications and monitoring for iatrogenic complications are usually most easily done in the mental health setting.

There is no formal psychiatric subspecialization for bipolar or other mood disorders. Any psychiatrist should be able to diagnose and manage bipolar disorder appropriately. However, groups that see a high volume of persons with bipolar disorder and have extensive experience with medication management of mood disorders may be in the best position to manage the more complex forms of the illness and to provide the most aggressive combination of pharmacologic and psychoeducation and psychotherapeutic management.

Afterward

Dr A spent 6 years in and out of treatment, including multiple hospitalizations with seclusion and restraint for manic episodes. His marriage ended in divorce during this time. He was

finally stabilized on a combination of three psychotropic agents. He has resumed medical practice, with his only continuing symptom a mild intention tremor due to lithium treatment. Drug and alcohol use was never a part of the clinical picture, save occasionally at the peak of manic episodes.

Ms B has continued to be bothered by bouts of depression, although these are less severe with appropriate titration of lithium and the occasional addition of bright light treatment for winter depressive episodes. She has had no further suicide attempts. She has continued to perform well professionally.

Mr C's whereabouts are unknown.

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Personality Disorders and Depression: An Overview of Issues and Findings

M. Tracie Shea, PhD

Personality disorders are defined . . . as enduring, inflexible, and maladaptive patterns of traits and behaviors that are typically manifested by the time of adolescence or early adulthood.

The introduction of a separate axis for diagnosis of personality disorders in the *DSM-III*, and the encouragement to diagnose multiple disorders when criteria are met, have resulted in an increased focus on comorbidity between personality disorders and various Axis I disorders, particularly depression.¹ Historically, personality features such as excessive interpersonal dependency, introversion, and obsessiveness have been theoretically and empirically associated with depression.² The frequent findings of high rates of concurrent diagnoses of many of the Axis II personality disorders with depression have led to a renewed interest in the role that problems in personality functioning play in the onset and course of depression. Questions of interest include the role of personality disorders in the etiology of depression, the possibility of etiologically distinct subtypes of depression defined by the presence of certain personality features and disorders, and the implications of personality disorders for the treatment of depression. Following a review of the current diagnostic conceptualizations of personality disorder, this paper will address each of these questions.

Personality Disorders

Personality disorders are defined by the *DSM* as enduring, inflexible, and maladaptive patterns of traits and behaviors that are typically manifested by the time of adolescence or early adulthood. To be considered a personality disorder, such traits and behav-

iors should be pervasive, occurring across a broad range of situations, and must be associated with persistent and significant impairment in functioning or personal distress. Disturbances are manifested in cognition (ie, perception of others, oneself, and events), affect (ie, frequency, intensity, and appropriateness of emotional arousal and expression), control over impulses, and interpersonal functioning.

The personality disorders have been grouped conceptually by the *DSM-III* and *DSM-III-R* into three clusters, based on similarity in features. These include: 1) paranoid, schizoid, and schizotypal personality disorders, characterized by odd or eccentric behavior; 2) histrionic, narcissistic, antisocial, and borderline personality disorders, characterized by dramatic, erratic, or emotional behavior; and 3) avoidant, dependent, obsessive-compulsive, and passive-aggressive personality disorders, characterized by anxious or fearful behavior.^{1,3} Each of the disorders is defined by a set of criteria, and diagnosis requires manifestation of a minimum number of the criteria by early adulthood in a variety of contexts, and significant impairment in social or occupational functioning or subjective distress.

Consistent with the medical model approach to psychopathology, the *DSM* has conceptualized personality disorders as syndromal, categorical constructs. This model for personality disorders has been increasingly questioned, however. Many of the traits of the personality disorders are extreme versions of normal personality traits (eg, dependency, introversion), which tend to be continuously rather than dichotomously distributed. Also, the common finding of high rates of diagnostic overlap among the personality disorders challenges the validity of the

personality disorders as distinct constructs.⁴ More basic dimensions likely underlie the personality disorder categories, and a several alternative schemes have been proposed for the personality disorders.⁵

Despite the unresolved issues regarding the optimal way to conceptualize personality disorders, clearly individuals with depression often are characterized by disturbances in personality functioning. In clinical samples of depressed patients (inpatient and outpatient), Axis II disorders are common, with most studies reporting 30% to 40% having concurrent personality disorders.⁶ Inpatient samples have higher rates of dramatic cluster personality disorders (particularly borderline and histrionic), perhaps a result of the impulsive behavior, including suicide attempts, which characterizes the dramatic cluster personality disorders.⁷⁻¹⁰ Outpatient samples, in contrast, tend to have more of the anxious-fearful cluster personality disorders (eg, avoidant, dependent, obsessive-compulsive)^{11,12} Although less frequently studied, the high rates of comorbidity also appear when samples have been defined or selected on the basis of personality disorder.⁶

While the reasons for the high rates of comorbidity are unclear, several hypotheses have been proposed, most of which involve speculations regarding etiologic or causal relationships among these disorders.^{13,14} It has of-

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ABBREVIATIONS USED

APA: American Psychiatric Association

DSM: Diagnostic and Statistical Manual

ECT: Electroconvulsive therapy

MAOI: Monamine oxidase inhibitor

REM: Rapid eye movement

ten been assumed, for example, that personality disorders play a causal role in depression, by representing a vulnerability that puts the individual at risk for developing depression. An individual with dependent personality disorder, for example, would be at risk for depression following the loss of an important relationship. In contrast, it has been proposed that the personality disturbance seen in individuals with depression may be the consequence of the experience of depression, particularly repeated, chronic, or severe forms of depression. Personality disorders have also been conceptualized as related but different manifestations of the same underlying disease process, thus existing on a spectrum. Others have argued that much of the personality pathology (eg, irritability, low self-esteem, unstable relationships) found in depressives is actually a manifestation of affective disorder.

It has also been proposed that the high rates of comorbidity may be due not to etiologic factors but rather to selectivity operating in treatment-seeking samples (ie, those with multiple disorders are more likely to end up in treatment). Findings of similar rates of personality disorders in individuals diagnosed with depression in non-treatment seeking samples, however, argues against this explanation.¹⁵ Finally, some of the comorbidity findings may be artifactual. Depression has been shown to distort assessment of personality: individuals tend to describe themselves as having more personality pathology when depressed than they do when well.¹⁶ It is also sometimes unclear whether the comorbid diagnoses reflect truly distinct disorders, or the result of overlapping criteria. For example, affective disturbances are part of the definition of borderline personality disorder, and it is unclear whether the depression that is common in individuals with borderline personality disorder is a distinct, "comorbid" disorder, or part of the borderline personality disorder.

Personality and Subtypes of Depression.—Personality features have long been associated with attempts to define etiologically based subtypes of affective disorder. The old notion of "neurotic" depression, believed to have "psychological" causes and to be associated with more "neurotic" person-

ality traits than "endogenous" depression is one example.¹⁷ More recent examples include several spectrum models of depression. A typology of affective disorders developed by Winokur incorporates familial patterns of psychopathology, including personality, to define subtypes of depression.¹⁸ "Depressive spectrum disease" is defined by the presence of alcoholism or antisocial personality in first-degree relatives of unipolar depressives; the alcoholism and antisocial personality disorder are believed to exist on a spectrum with this subtype of depression. "Pure depressive disease," in contrast, is defined by the presence of depression and the absence of alcoholism and antisocial personality in relatives. Characteristics associated with depressive spectrum disease include earlier age of onset of depression, female gender, personality problems including unstable relationships, irritability, nervousness, and demandingness, and a more variable course of depression.

A similar subset of depressed patients has been defined on the basis of chronic characterologic problems.¹⁹ "Character spectrum disorder" is marked by various unstable traits, including dependent, histrionic, antisocial, or schizoid features, irritable dysphoria, and substance abuse, as well as by a family history of alcoholism or antisocial personality disorder. The unstable personality traits and associated pathology are believed to be the result of unstable and chaotic developmental experiences. The depression is presumed to be secondary to the personality disturbances, and its etiology is hypothesized to be distinct from that of true affective disorder. Character spectrum disorder also has been characterized by a lack of response to somatic therapies and by an absence of the biological markers of depression (such as REM latency and abnormal dexamethasone suppression).¹⁹

Studies comparing depressed patients with and without personality disorders on various features have tended to show differences compatible with the above formulations. Depressed patients with personality disorders have been found to have a younger age of onset of depression, more frequent separation and divorce, and/or more familial alcoholism and

sociopathy.^{7,10,12} Some of these studies have also found depressed patients with personality disorders to be characterized by less frequent dexamethasone non-suppression, compared to patients with depression alone.^{7,10}

Implications for Treatment

Studies reporting on types of treatment received in naturalistic settings reflect the clinical belief that depressed patients with personality disorders will be unresponsive to somatic treatments. Charney et al reported that 71% of depressed inpatients without a diagnosis of personality disorder were treated with medication, compared with 28% of those with a personality disorder diagnosis.⁸ Both groups were equally likely to receive psychosocial treatments. Other studies have found that depressed personality disorder patients are less likely to receive electroshock therapy.^{7,20}

Studies investigating the influence of personality disorders on response to somatic treatments have tended to support the notion that these patients do less well than those without personality disorders.⁶ While the studies are nearly all naturalistic, they consistently indicate a poorer response to tricyclic antidepressants.^{7,8,10} Some studies also suggest a poorer response to ECT for these patients, although these findings are less consistent.²¹

In contrast, a few studies have suggested that depressed patients with certain types of personality features may show a selectively good response to monoamine oxidase inhibitors (MAOIs).²²⁻²⁴ The patients in these studies have been characterized by features of borderline personality disorder, including an extreme vulnerability to rejection that precipitates depressive episodes, unstable and chaotic relationships, difficulty being alone, chronic feelings of emptiness, and impulsive-destructive behavior. The MAOI phenelzine was found to be more effective than placebo as well as imipramine for these patients.^{23,24}

Also of interest are the findings from four small open trials of fluoxetine in the treatment of patients with borderline or antisocial personality disorders.²⁵⁻²⁹ Besides improvements in depressed mood, fluoxetine appeared effective in treating impulsivi-

ty and aggression in these patients. Placebo-controlled studies will be important to confirm these findings.

Studies also have suggested that depressed patients with personality disorders respond less well to some forms of psychosocial treatments.⁶ In a randomized clinical trial of the comparative efficacy of interpersonal therapy, imipramine plus clinical management, and placebo in the treatment of depression, patients with personality disorders tended to have a poorer outcome in all the conditions except cognitive therapy, in which they seemed to do as well or slightly better.^{30,31} Other studies have reported a worse response for depressed patients with personality disorders patients treated with behavior or psychodynamic therapy, and with eclectic therapy.^{32,33} However, Simons et al reported a comparable response to cognitive therapy for patients with and without personality disorders.^{31,34}

The general and more common finding of worse treatment outcome for patients with personality disorders does not mean that these patients do not benefit from treatment, as they frequently show significant improvement. They just tend to show less improvement than those without personality disorders. Given that these patients generally have a history of more chronic or recurrent depression, as well as less stability in their relationships and lives in general, it is not surprising that they do not respond as quickly or fully as depressed patients with less complicated pathology. This point is particularly relevant given that all the controlled studies investigating this question have been short-term (ie, 16 weeks or less). The increasing evidence that patients with depression need longer treatments may be particularly true for those with personality disorders.^{35,36}

Treatment for these patients needs to focus on the maladaptive patterns of behaviors and traits that are present, as well as the depression. Many of the psychosocial treatments developed for depression could be applied on a longer-term basis for these patients. The use of cognitive therapy for all the Axis II disorders, for example, has been described including the application of cognitive strategies and techniques to address the specific kinds of

dysfunctional thoughts and assumptions associated with each of the personality disorders.³⁷ Similarly, interpersonal and behavioral approaches can be directed at the specific kinds of disturbances in interpersonal and behavioral patterns that are characteristic of personality disorders.

Future Directions

While the etiologic relationship between personality disorders and depression is uncertain, clearly the presence of enduring maladaptive traits and behaviors have an important impact on treatment response and course of depression. Understandably, most of the existing research has followed the Axis II model, defining personality disorders syndromally and categorically. However, this classification system for personality disorders, still in an early stage of development, is characterized by numerous conceptual and methodological uncertainties. Given the extent of overlap among the personality disorders, it is likely that more basic dimensions underlie these disorders, and recent research has demonstrated the value of assessment of such underlying dimensions. It has been demonstrated, for example, that serotonin dysfunction correlates better with the specific dimension of impulsive aggression than with a categorical diagnosis.³⁸ Also notable is a similar finding that borderline personality disorder is more highly associated with a family history of impulsive aggressive behaviors than with a family history of a borderline diagnosis.³⁹ It is likely that specific dimensions of behavior or pathology will be more important than categorical diagnoses of personality disorder in predicting response to specific forms of treatment, as well as in the search for etiologic factors. Research directed at elucidation of such more specific and theoretically relevant dimensions of psychopathology should lead to a clearer understanding of the complex relationship between personality disorders and depression, and to increased knowledge regarding optimal treatment strategies.

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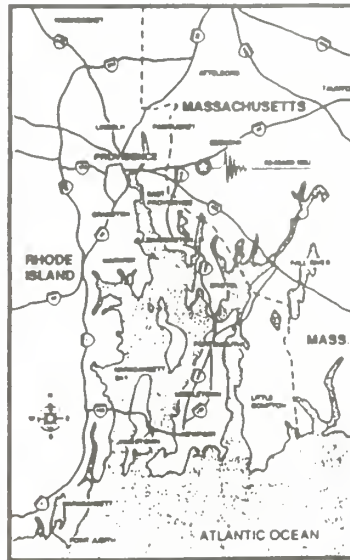
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Depression and Substance Abuse

Timothy I. Mueller, MD

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27% of people with a lifetime diagnosis of major depressive disorder will have an additional lifetime diagnosis of substance abuse or dependence. Conversely, 11.8% of substance-abusing or dependent people will have a lifetime diagnosis of major depressive disorder.

"Which came first, the chicken or the egg, the egg or the chicken, or the chicken or the egg."

Children's Nursery Rhyme

Alcohol and drug use disorders and depressive disorders often occur in the same person. Physicians often will see patients with a substance use disorder who also have symptoms of depression, symptoms of anxiety, and a whole array of medical conditions that are often complications of substance use. The Epidemiologic Catchment Area Survey (ECA) showed a lifetime prevalence of Major Depressive Disorder (MDD) of 5.9% and a lifetime prevalence of any substance use disorder of 16.7%.¹ These conditions frequently will appear together in a busy practice. Research further shows that 10% to 30% of people presenting for a broad range of psychiatric disorders will have an additional diagnosis of alcohol dependence^{2,3} and 8% to 70% of alcoholics report significant depressive symptoms.⁴⁻⁷ The population-based data from the ECA using more narrowly focused diagnostic *DSM-III* categories indicate that 27% of people with a lifetime diagnosis of MDD will have an additional lifetime diagnosis of substance abuse or dependence.

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Conversely, 11.8% of substance abusing or dependent people will have a lifetime diagnosis of MDD.¹ Because of sheer numbers the two syndromes are important clinically for the practicing physician.

The knowledge that the two disorders often occur together, however, does not help to differentiate them. The children's conundrum quoted above crystallizes the dilemma. Difficulties in diagnosis frequently arise since the symptoms of alcohol and drug intoxication and withdrawal overlap with the symptoms that are part of the diagnostic criteria for depressive disorders.⁸ Table 1 presents the diagnostic criteria for Major Depressive Disorder as outlined in *DSM-III-R*. Not only does the pharmacologic action of alcohol and other drugs confuse the picture, but when people misuse substances they also create problems in their life that may contribute to or exacerbate depressive symptoms and depressed mood.

An additional source of diagnostic difficulty rests with the fact that each disorder is itself susceptible to its own potential lack of diagnostic clarity. The term depression can be used to refer to a mood state, a cluster of symptoms, or a syndrome. When various self-report measures such as the Beck Depression Inventory are used for assessment, depressive symptoms can vary along a continuum from not depressed to extremely depressed. However, as noted above, the diagnosis of MDD requires the presence of a specific collection of symptoms. Similarly, alcohol and drug problems can be seen as varying on a continuum. The *DSM-III-R* diagnostic criteria for substance abuse and dependence require specific symptoms to be present (Table 2). Thus when reports of the co-occurrence of alcoholism and de-

pression have such a wide range, it is crucial to be mindful of the potential uncertainty in the diagnosis of each condition.⁹

The fact remains that the two disorders do co-occur frequently, and several mechanisms have been offered to explain this relationship. The self-medication hypothesis championed by Khantzian¹⁰ represents the commonly reported experience of patients who say they use medications to treat their uncomfortable feeling states. Recent work by Weiss et al¹¹ demonstrates that the majority of drug-abusing patients use their medication to treat depressive symptoms. The two disorders may also be two faces of a common vulnerability to mental health problems. The depressive spectrum hypothesis of Winokur¹² is based on the finding that in family studies, women with a family history of depression are at greater risk for depression and alcoholism than women who do not have such a history.

For the clinician this co-occurrence has diagnostic, prognostic, and therapeutic implications.

Diagnostic Implications

The overlap of psychoactive drug intoxication and withdrawal symptoms with those of MDD often leads to some confusion. Alcohol, barbiturates, opioids, and benzodiazepines are sedatives, and people who actively use these chemicals often experience low mood, low energy, and decreased libi-

ABBREVIATIONS USED

DSM: Diagnostic and Statistical Manual

ECA: Epidemiological catchment area

MDD: Major depressive disorder

REM: Rapid eye movement

do. These depressive symptoms are among the diagnostic criteria for depression but do not necessarily signify the presence of a MDD.

The clinical features of depression, in particular changes in affect, cognition, behavior, physical functioning, and somatic functioning, may present a confusing picture in the dually diagnosed patient. The cognitive features usually associated with depression—cognitive slowing and negative thought content—may be equally present in the active substance user. The cognitive slowing of chronic alcoholism or chronic use of marijuana may be confused with the cognitive slowing of depression patients. Similarly, social withdrawal, which is seen both in alcohol and drug-abusing patients, is also seen in depressed patients. Likewise, changes in libido and impairment of sexual performance may be a marker for drug dependence as well as depression.

The somatic symptoms of sleep and appetite disturbance that are hallmarks of MDD, are also seen in substance abusers limiting the diagnostic specificity of these symptoms. Appetite disturbance and weight change may be affected by substance use. Active alcoholics often experience a loss of appetite with weight loss. The typical findings of sleep disturbance in depression (ie, decreased total sleep time with early morning awakening) may be masked or missing. For example, an active alcoholic's sleep disturbance usually follows a fragmented pattern; the active alcoholic is able to fall asleep but wakes in about 4 hours, sometimes after a disturbing dream. This pattern results from the initial sedative effects of alcohol, the consequent delayed REM latency and the acute onset of withdrawal symptoms. Alcoholics in early remission may complain of sleep disturbances persisting through the first year of sobriety. Generally these complaints involve difficulty falling asleep and intense nightmares. Thus sleep disturbance, one of the traditional markers of MDD, may not be a reliable diagnostic guide in the active or recovering alcoholic. Conversely these symptoms, which actually can be a reflection of current or past alcohol use, may be incorrectly attributed to MDD. Similar arguments apply to other short-acting sedatives such as the

Table 1.—Major Depressive Disorder

DSM-III-R Diagnostic Criteria*	
A. At least five of the following symptoms have been present for two weeks with at least one symptom from #1 or #2.	
1. Depressed mood	
2. Anhedonia - Markedly diminished interest or pleasure in life activities	
3. Significant weight loss or gain or significant appetite increase or decrease	
4. Insomnia or hypersomnia	
5. Psychomotor retardation or agitation	
6. Anergy - loss of energy	
7. Worthlessness or excessive guilt	
8. Loss of concentration	
9. Recurrent thoughts of death or suicide	
B. There is no known organic cause for the mood state	
C. Delusions or hallucinations, if present, occur in the presence of the mood disturbance.	
*Adapted from American Psychiatric Association, 1987 ²⁹	

opioids, short half-life benzodiazepines and barbiturates.

Depression itself is frequently underdiagnosed in primary care settings because many patients with MDD present not with complaints of sadness but with somatic symptoms. Many primary care physicians are sophisticated in recognizing that complaints of constant fatigue, headaches or gastrointestinal disturbances are markers

... women with a family history of depression are at greater risk for depression and alcoholism than women who do not have such a history.

for affective disturbances. However, these complaints are also reflective of chronic or even acute substance use, particularly alcohol. Chronic fatigue may result from the sleep disturbance associated with depression or with alcohol as described above. Severe acute or chronic headaches may reflect an underlying physiological disturbance unrelated to depression or substance use; however, many substance users have ongoing cycles of intoxication and withdrawal that may provoke complaints of migraine or cluster headache symptoms. Indeed, the migraineur who has depleted a prescription of Fiorinal or similar medication may be dependent on the sedative component of the medication and may be engaging in multiple addictive behav-

iors to obtain a sufficient supply of the sedative. Gastrointestinal disturbances are a frequent consequence of alcohol use as well as mood disorders.

Alcohol and other sedative withdrawal, though typically an adrenergic overflow syndrome with tremor, shakiness, sweating, low grade fever, irritability and the risk of convulsions, also are often manifested by the same overlap symptoms of sleep disturbance, anorexia, and mood lability. There is less diagnostic overlap with the opioid withdrawal syndrome, which is characterized by irritability, agitation, myalgias, gastrointestinal disturbances, sweats and tremor, although withdrawal-related mood lability often can be interpreted as part of a depressive disorder. The converse applies to the stimulants and cocaine where intoxication is characterized by hyperactivity and stimulation, whereas the withdrawal period and detoxification are largely characterized by symptoms that are often indistinguishable from MDD. These symptoms include sadness, anxiety, sleepiness and low energy.¹³

To clarify this confusion, leaders in the field often attempt to distinguish syndromes by primary versus secondary characteristics.⁸ Most typically, the label "primary" is attached to the disorder that occurs first in the patient's life with the implication that the secondary disorder is a consequence of the earlier disorder. Although the chronological timing may not have validity when used to explain causal

relationships, it is often the case that a primary alcoholic will clinically "behave" most like an alcoholic with no other co-occurring disorders. It may also be true that the primary/secondary distinction has some implications in terms of heredity, in that primary alcoholism may be more heritable.¹⁴

Prognostic Implications

Epidemiologic studies have examined the prognostic implications of the co-occurrence of the two disorders from the standpoint of the individual who presents with depression or the individual who presents with a substance use disorder. For the clinician, this distinction is arbitrary since we usually see patients with both problems. However, there are implications for prevention insofar as we can be alert for early signs of the development of one or the other disorder and possibly intervene to decrease the increased morbidity that accompanies the co-occurrence of the two disorders.

The integration of the epidemiologic data demonstrates that the combination of depression and substance abuse is "double trouble." The combination of depression and substance abuse places patients at an increased risk for suicide.¹⁵ In addition, people with MDD and alcoholism have poorer long-term spousal relationships than non-alcoholic depressives.¹⁶ Generally, the level of global severity of psychiatric disturbance appears to be directly associated with the outcome in alcohol and drug treatment: the more severe the psychopathology, the worse the outcome.¹⁷ However, there is some suggestion of gender specificity, with depressed male alcoholics having a worse prognosis than their non-depressed counterparts, and depressed female alcoholics having better outcomes than nondepressed female alcoholics.¹⁸

This discussion of long-term prognostic implications must also recognize that the majority of depressive symptoms resolve with abstinence. It is crucial to keep in view this short-term perspective. The frequently cited study by Brown and Schuckit⁴ showed that 40% of male veterans newly admitted for inpatient alcohol treatment demonstrated signs and symptoms of

Table 2.—Psychoactive Substance Abuse and Dependence

DSM-III-R Diagnostic Criteria*

Psychoactive Substance Abuse

1. Either (a) or (b) has persisted for a minimum of 1 month:
 - a. Continued use despite adverse life consequences
 - b. Recurrent use in hazardous situations
2. Has never had the diagnosis of dependence

Psychoactive Substance Dependence

At least three of the following have persisted for a minimum of 1 month or have occurred repeatedly over a longer period:

1. Substance taken in excess of person's intent
2. One or more attempts to cut down
3. Significant time spent obtaining, experiencing effects of or recovering from effects of substance
4. Intoxication or withdrawal in hazardous situations or situations of responsibility
5. Significant changes in life activities due to substance use
6. Continued use despite adverse life consequences
7. Tolerance to drug effects
8. Characteristic withdrawal syndrome
9. Substance taken to relieve or avoid withdrawal symptoms

*Adapted from American Psychiatric Association, 1987²⁹

significant depression as determined by the Hamilton Depression Scale. After 4 weeks of abstinence and no specific treatment for depression, this fraction dropped to 6%.

Therapeutic Implications

Historically there have been two camps in the treatment community, each righteously defended by its adherents. The mental health and psychiatric community stereotypically has suggested that treating the underlying psychiatric disorder will resolve the substance use disorder. Conversely the alcohol and drug treatment field defends the argument that the psychopathology is secondary to the drug use disorder. In recent years there has been a moderation of the two positions. However, the practicing clinician may be presented with one or the other dogma.

Since the majority of depressive symptoms seen in the intoxicated or withdrawing substance abusers will resolve with time and sobriety, an initial focus on alcohol and drug abstinence will be the most efficacious. For the severely depressed or suicidal patient, this often means detoxification and treatment in the hospital to keep the patient safe during the grueling phase of detoxification and early abstinence. Fortunately the treatments for both disorders are similar and efficacious, and rarely does the treatment

of one disorder preclude the simultaneous treatment of the other. Although the patient may not respond well to psychotherapy while detoxifying, and specific cognitive therapies may not be indicated during initial withdrawal due to cognitive impairment, the therapeutic milieu and support, often called the social setting, can powerfully decrease the intensity of the withdrawal syndrome¹⁹ and substantially alleviate the depressed mood. In alcohol and drug-using patients who are suicidal, psychotherapy and milieu are effective in decreasing this high risk symptom mediated in part by nonspecific therapeutic factors. The 12-step message embodied in Alcoholics Anonymous and other self-help groups can support ongoing psychotherapy for depression. Once the substance abusing patient has achieved abstinence, nonpharmacologic therapies such as cognitive therapy, social skills training, assertiveness training and behavioral therapies can be very effective in treating both the substance abuse and depression.

There are no uniform pharmacologic recommendations in this clinical setting. A rule of thumb is to avoid treating depressive symptoms and suspected depressive disorders until a person has had at least 4 weeks of sobriety. The exceptions to this rule would occur in patients who have well-documented recurrent bipolar or major depressive disorder that occur dur-

ing periods of sobriety, or in patients with a strong family history of either disorder. In these cases it is often advisable to begin drug therapy early.

Partly motivated by the self-medication hypothesis, specific anti-depressant therapies have been examined as adjuncts in the treatment of alcoholism. The results have been disappointing.⁷ Lithium once was popular but has not held up to scientific inquiry. There is no evidence that it enhances sobriety. Likewise tricyclic antidepressants have been used with no compelling results. Even studies where tricyclic antidepressants were used to treat depressive symptoms successfully, were flawed in that treatments were applied during the active detoxification phase. In this context it was not possible to tell if the medication or sobriety itself was responsible for the improvement in depressive symptoms.

... 40% of male veterans newly admitted for inpatient alcohol treatment demonstrated signs and symptoms of significant depression ...

Tricyclic antidepressants, bromocriptine, and amantidine, because of their salutary effects on the catecholamine neurotransmitter system have been tried in the treatment of cocaine dependence. Long-term cocaine use depletes catecholamines, and it is postulated that this depletion is an important feature in the drug user's craving for cocaine and subsequent relapse. Short-term studies have shown these drugs to be of some value in assisting abstinence and combating craving, but it is unclear what the long-term effectiveness of these agents will prove to be.²⁰

As a rule benzodiazepines should be avoided in this population. While there may be mixed evidence about whether alcoholics and drug-abusing people have a unique or increased risk for abusing prescribed benzodiazepines,²¹ most clinicians have had the experience of seeing patients abuse the drugs prescribed to treat symptoms of anxiety or insomnia. For patients with MDD and a substance use disorder there is little role for the use of benzodiazepines and other seda-

tives. This caution is especially warranted since benzodiazepines are the most commonly prescribed medications for outpatient depressions. The anxiety and sleep disturbance of MDD generally respond well to antidepressant therapies. In patients with confidently diagnosed MDD, the co-occurrence of a substance abuse disorder presents no special cautions except if severe liver impairment is present in which case lower doses and blood level monitoring of the tricyclic antidepressants is advised. Generally, the broad range of available pharmacotherapies and psychotherapies, as described in this issue, are efficacious. (See Keitner and Miller, this issue.) Electroconvulsive therapy is effective for treatment-resistant depressions, and there are no specific contraindications for its use in people with alcohol and drug use disorders.

Tobacco Dependence

Tobacco dependence also has been associated with depression. This relationship has been demonstrated both in population surveys and in smoking cessation treatment outcome research.²² For example, among the general population of adults in the US, smokers with MDD or depressive symptoms are less likely to quit smoking than nondepressed smokers, and smokers report higher levels of depression than nonsmokers.²³ This association between depression and smoking appears to be robust across age and ethnic groups.

Since depressed mood, depressive symptoms or a history of MDD may interfere with successful smoking cessation, it may be important to address the issue of depression with some smokers to help them successfully quit smoking. There is, in fact, some preliminary evidence that treatment of depression aids in smoking cessation. Doxepine hydrochloride, a tricyclic antidepressant, has been shown to decrease nicotine withdrawal symptoms.²⁴ Similar results have been demonstrated with nortriptyline and fluoxetine. There is also preliminary evidence that pretreatment with antidepressants may prevent the development of abstinence-related depressive symptoms in smokers with a history of a depressive disorder.²⁵ While more

research is needed in this area, these preliminary data suggest that the treatment of depression (in this case pharmacologic treatment) may augment the likelihood of successful smoking cessation.

The acquisition of specific skills for coping with depression could also help prospective quitters in several ways. These skills could help to prevent the onset of depressive symptoms upon cessation from smoking and modify or improve affect in potential negative mood situations, which are the most common precipitants of relapse.²⁶ Currently, treatments focus primarily on the acquisition of coping skills to deal with temptations to use and high-risk situations for relapse, and minimally if at all, on dealing with depression. This state of affairs may contribute to the disappointing outcomes in smoking cessation. Hall et al²⁷ have presented smoking cessation treatment data comparing a cognitive-behavioral intervention designed to enhance affect regulation to a health education control condition, with all subjects receiving nicotine gum (2 mg). Their results suggested that the affect regulation treatment may be specifically efficacious in supporting smoking cessation for smokers with a history of major depression (50% abstinence at 6 months vs 12% for the health education control).

... avoid treating depressive symptoms and suspected depressive disorders until the person has had at least 4 weeks of sobriety.

Smokers with a history of MDD appear to be more likely to experience depressive symptoms upon initial cessation and are more likely to be unsuccessful in their effort to remain abstinent. We recommend that antidepressants be considered as an adjunct to smoking cessation treatment when: 1) there is a history of MDD; 2) previous smoking cessation attempts were associated with prominent depressive symptoms, especially if they persisted beyond the first 2 weeks of abstinence; and 3) previous attempts at cessation using behavioral interventions and other pharmacologic agents

have failed.

Finally, smoking is known to accelerate the metabolism of many drugs, among them being imipramine, a tricyclic antidepressant.²⁸ Because metabolic effects of cigarette smoking are complex, it is difficult to generalize about the effects of cigarette smoking on entire classes of drugs. For example, though cigarette smoking increases the metabolism of imipramine, it has minimal or no effect on the metabolism of nortriptyline. While the full significance of the effects of smoking on drug metabolism and pharmacodynamics is unclear, one corollary is that it may be necessary to prescribe higher doses of certain drugs, such as imipramine, in patients who smoke, and when smokers taking such drugs quit smoking, drug toxicity may occur.

Conclusion

Depressive disorders and substance use disorders including tobacco dependence are highly comorbid and co-occur with great regularity. Clinicians need to consider both together in patients who are presenting for the other condition. The diagnosis can be difficult but partial depressive syndromes do appear to respond to abstinence. Full syndromes may also improve with control of the alcoholism. Poorer alcohol and drug use outcomes are related to degree of psychopathology suggesting the need to treat the psychopathology to improve the substance use disorder. In reality both disorders probably need to be treated together to maximize the likelihood of improvement. Clinicians need to be aware of and comfortable with the broad range of psychopharmacology, psychotherapy, self-help and 12-step programs, family therapy, and the need to avoid sedatives for the treatment of depression or anxiety in the substance-abusing patient.

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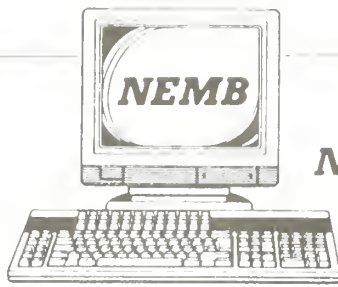
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Combined Psychopharmacological and Psychosocial Treatment for Depression

Gabor I. Keitner, MD

Ivan W. Miller, PhD

Pharmacotherapy, although more suited to a "cookbook" approach than psychotherapy or family therapy, still requires adherence to certain management principles, whether used by itself or in combination with psychosocial treatments.

Introduction

A number of therapies—medications, individual psychotherapies, group psychotherapies, and family and marital therapies—have been demonstrated to be efficacious in treating depressed patients. However, it is becoming evident that none of these treatments by itself is sufficient for every depressed patient. Thus, clinicians and researchers are turning increasingly toward combining these therapies for optimal treatment.

Psychopharmacological Treatment

Pharmacotherapy alone will produce a clinical response in 40% to 70% of patients and a remission rate in only 30% to 40%.¹ Rates of response and remission are similar for monoamine oxidase inhibitors (MAOIs) and the selective serotonin reuptake inhibitors (SSRIs).

Pharmacotherapy, although more suited to a "cookbook" approach than psychotherapy or family therapy, still requires adherence to certain therapeutic management principles, whether used by itself or in combination with psychosocial treatments. A pharmacotherapy treatment approach that

is consistent and systematic most likely will provide the optimal set of circumstances for the drugs to exert their therapeutic effect while minimizing the likelihood of haphazard and inadequate treatment trials.

A systematic pharmacotherapeutic approach should involve the following steps: 1) establish the proper diagnosis; 2) establish the presence or absence of psychosis; 3) make sure that comorbid illnesses are treated simultaneously; 4) determine the level of severity and the need for hospitalization; 5) choose antidepressants to match the patient's target symptoms with the drug's side effect profile; 6) start with monotherapy; 7) give maximum therapeutic doses; 8) give the drug long enough to be able to determine efficacy; 9) employ systematic polypharmacy for treatment-resistant episodes; and 10) ensure maintenance treatment (see Table 1).

Treating the Acute Episode

It is essential to establish an accurate diagnosis before initiating antidepressant treatment and to determine that the patient indeed has a depressive episode of sufficient intensity and duration to respond to the drug. The presence of a full neurovegetative syndrome, a level of severity that leads to functional impairment, and persistence of symptoms for 2 to 4 weeks are reasonable indicators for a trial of antidepressant drugs.^{2,3} It is also important to determine whether the current depressive episode is the depressed phase of a bipolar illness. Although bipolar depression will respond to pharmacotherapeutic agents similarly to unipolar depression, it is important to be aware of and to anticipate the

possibility of precipitating a manic episode with the antidepressant drugs used.

The next step is to determine the presence or absence of psychotic symptoms including delusions or hallucinations. Patients who have major depression with delusional symptoms tend to have a poor response to antidepressant drugs alone and will do better with a combination of neuroleptic and tricyclic antidepressants.⁴ Electroconvulsive therapy is another effective alternative for these patients.

Comorbid conditions, whether psychiatric or medical, need to be identified and treated simultaneously. Common comorbid conditions such as personality disorders, substance abuse, anxiety disorders and a variety of medical conditions—most commonly, cardiovascular and neurologic dysfunction—will likely impair the recovery process and therefore need to be treated simultaneously with the affective disorder.⁵⁻⁷

Antidepressant drugs should be chosen to match the patient's target symptoms with the drugs' side effect profile, thereby maximizing potentially beneficial side effects and minimizing unwanted side effects. Choosing pharmacologic agents to deal with target symptoms decreases the necessity of combining drugs for different target symptoms. Drugs that maximize beneficial effects while minimizing adverse experiences can usually be found

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ABBREVIATIONS USED
MAOI: Monoamine oxidase inhibitor
SSRI: Selective serotonin reuptake inhibitor
TCA: Tricyclic antidepressant

(see Table 2).

There are four broad classes of antidepressants to choose from: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and atypical antidepressants (such as trazodone and bupropion). Table 2 outlines some of the common side effects of antidepressants as well as their usual dose ranges. All of these antidepressants generally are equivalent in efficacy although an individual patient may respond preferentially to one agent over another.

Choosing an antidepressant should depend on the patient's target symptoms, the medication's side effect profile, the patient's previous history with the antidepressant agents, and family history of response with any of the antidepressant agents. The cost of the medications may be another significant factor. Generally, for patients on whom there is little new information, it makes sense to match the patient's target symptoms with the appropriate side effect profile.

For example, depressed patients with agitation and insomnia may initially do better with sedating antidepressants (eg, amitriptyline, imipramine or trazodone) while depressed patients with anhedonia, anergia and psychomotor retardation may do initially better with drugs such as desipramine or

Table 1.—Principles of Pharmacological Treatment

- establish diagnosis
- determine presence or absence of psychosis
- treat comorbid conditions
- assess need for hospitalization
- choose antidepressant to match target symptoms
- start with monotherapy
- give maximum therapeutic doses
- trial of 4-6 weeks to establish efficacy
- maintenance therapy

the SSRIs such as sertraline or fluoxetine. Although there is no data that such matching between target symptoms and side effect profiles will lead to quicker or more effective treatment, by making the patient more comfortable and by minimizing the likelihood of multiple side effects, the patient may comply with the treatment more readily.

It makes sense to start with monotherapy in nonpsychotic, unipolar major depressions. There is an increasing tendency in psychiatry to mix medications to address a variety of different symptoms. It is now common practice to combine, for instance, trazodone with fluoxetine, or minor

tranquilizers with a tricyclic antidepressant in an attempt to deal with the multitude of symptoms that are part of the depression. Polypharmacy may be an appropriate course for treatment-resistant patients but may also create as many problems as it solves. Polypharmacy may not only make it difficult to establish the necessary therapeutic range of the active therapeutic agent but may also suppress target symptoms (for instance, insomnia) that most clearly indicate the course of the underlying depressive disorder. Polypharmacy, in addition, may increase the number of significant side effects and make the patient feel the depression was particularly difficult to treat. Explaining the reasons for starting with monotherapy and being reassuring about the likelihood of response over a reasonable period usually provides sufficient basis to engage the patient's cooperation in initial monotherapy.

If one antidepressant is to be used, then clearly it should be given in sufficient dosage to ensure the likelihood of its efficacy. The maximum doses tolerated by the patient within therapeutic blood level guidelines should be used. At least, the physician can be sure at the end of a therapeutic trial that that particular antidepressant had not worked.

It is also necessary to give the drug long enough to be able to determine

Table 2.—Side Effects of Antidepressants^{25,43,55}

Antidepressants	Sedation	Insomnia	Anticholinergic Effects	Orthostatic Hypotension	Nausea	Dose/Range (mg/d)
Amitriptyline	+++	0	+++	+++	0	100-300
Amoxapine	+	+	+	++	0	200-300
Bupropion	0	++	0	0	+	200-450
Desipramine	+	+	+	+	0	100-300
Doxepine	+++	0	++	+++	0	100-300
Fluoxetine	0	++	0	0	++	20-60
Imipramine	++	0	++	++	0	100-300
Maprotiline	++	0	+	++	0	100-200
Nortriptyline	++	0	+	+	0	75-150
Phenelzine	+	+	0	+++	0	30-90
Protriptyline	+	++	++	+	0	15-60
Sertraline	0	+	0	0	++	50-200
Trazodone	+++	0	0	++	+	200-600
Tranlycypromine	0	++	0	+++	+	20-60
+++ = Major Side Effects ++ = Moderate Side Effects + = Minor Side Effects 0 = None						

efficacy. Reasonable therapeutic trials of antidepressants should range from 4 to 6 weeks at therapeutic doses before concluding that they are not effective for a given patient.^{1,2,4,8} If the patient deteriorates or becomes suicidal during this period, a more rapid adjustment of the pharmacological approach is appropriate. There is a fine balance between excessively aggressive initial treatment versus a too passive expectant therapeutic stance. That is the art of pharmacotherapy. A systematic increase in dosage of one active antidepressant with careful monitoring of treatment will be effective for most patients, particularly if the pharmacotherapy is supplemented by psychosocial treatments.

Therapeutic Drug Monitoring

Therapeutic monitoring of plasma concentrations of the various antidepressants may be helpful in certain situations to ensure a maximum treatment trial. Therapeutic drug monitoring, however, is not indicated for all cases or for all antidepressant medications.

Well-defined plasma concentration response relationships are available for only a few antidepressants.⁹ Nortriptyline has the most clearly defined therapeutic window within which clinical response is likely to be optimal. There is some evidence for a plasma concentration relationship for desipramine, imipramine and amitriptyline although to a lesser degree than for nortriptyline. Atypical antidepressants, such as bupropion and trazadone, as well as the SSRIs, have not yet had adequate concentration response studies to determine therapeutic ranges.

Therapeutic drug monitoring is most useful in assessing compliance. Checking blood levels in those patients where there is suspicion of non-compliance at least indicates to the therapist whether the patient is taking the medications and to the patient that the therapist will be monitoring drug ingestion in a systematic way. For those drugs where there is an established plasma concentration response relationship, therapeutic drug monitoring can help improve therapeutic response by allowing dosage to be adjusted relative to the plasma con-

Table 3.—Treatment Options for "Resistant" Depression

- reevaluate diagnosis, compliance and comorbidity
- combine pharmacotherapy with psychotherapy and/or family therapy
- increase the dose and duration of pharmacotherapy
- augment with lithium
- switch antidepressants
- augment with T3
- switch to MAOI
- supplement with anticonvulsants
- ECT

centration. Avoiding toxicity is another use for drug monitoring. Particularly for those patients who are experiencing severe side effects on seemingly low doses, blood levels can help to determine whether even lower doses are achieving significant plasma concentrations. Conversely, patients on maximum doses of antidepressants with low side effects may, with therapeutic drug monitoring, be given even higher doses of the antidepressant with a greater sense of safety.

Treatment-Resistant Episodes

It is difficult to determine what proportion of patients with major depression are truly treatment-resistant. Much depends on the definition of what constitutes poor response and what constitutes adequate treatment. Poor response can mean the persistence of a wide range of symptomatol-

Table 4.—Characteristics of Effective Psychosocial Treatments for Depression

- time limited
- explicit rationale for treatment
- therapist is active and directive
- focus on current problems
- emphasis on changing current behavior
- self monitoring of change and progress
- regular homework assignments

ogy while there is no clear consensus on what constitutes adequate treatment. Nonetheless, it is generally accepted that from 10% to 30% of patients continue to experience significant depressive symptoms in spite of reasonable pharmacotherapy. A number of different models are available as algorithms for the treatment of such patients.^{2,10} A simplified systematic approach towards treatment-resistant patients follows (see Table 3).

Before undertaking more intrusive and complicated treatment procedures it is worthwhile to reevaluate the accuracy of the diagnosis, the likelihood of the patient's compliance with the first line of treatment, and to ensure again that there is no coexistent medical or psychiatric illness that has not also been adequately addressed.

It is important to emphasize that treatment resistance may be due to insufficient attention to intrapsychic and interpersonal aspects of the depression. Most algorithms for treatment resistance in the literature focus exclusively on seeking a combination of medications that will trigger remission. Although this may happen, we suspect that a systematic combination of pharmacotherapy with psychosocial treatments is more likely to be consistently effective for a greater number of patients.

The simplest steps to take with treatment-resistant depressions are to increase the drug dosage to the maximum level and to ensure that the therapy has been provided for a long enough period. If the patient is not suicidal and if the functional incapacity is not severe, extending the treatment trial for a few weeks at higher dosage levels may be all that is needed to effect a satisfactory response.

If non-response continues, a number of alternatives can be considered: augmentation with lithium, switching antidepressants, augmenting with T3, use of MAO inhibitors, supplementing treatment with anticonvulsants, and electroconvulsive therapy.

We prefer to use lithium augmentation when there is non-response to adequate therapeutic doses over a sufficiently long period of treatment. Lithium augmentation is effective in approximately 50% of patients for whom it is prescribed.¹¹ A major advantage is that it is likely to work relatively

quickly in those patients in whom it is effective.¹² The side effects of such treatment are readily tolerated; lithium may also be a useful maintenance treatment for those patients with frequently recurring episodes.

Switching to a different antidepressant in a different class is an obvious alternative, for instance, an SSRI in place of a TCA or the reverse. Within TCAs, if antidepressants are switched, it makes sense to choose an antidepressant acting on a different neurotransmitter system. For instance, switching from amitriptyline, which acts more on the serotonergic system, to desipramine, which acts more on the noradrenergic system.

There is some evidence that augmentation with T3 is helpful with certain depressed patients, particularly with women, and with patients who have subclinical hypothyroidism.¹³ Generally, augmentation with T3 appears to be somewhat less effective than the use of lithium.

... it is important to be aware of and to anticipate the possibility of precipitating a manic episode with the antidepressant drugs used.

Monoamine oxidase inhibitors, in spite of their potential difficulty with dietary restrictions and orthostatic hypotension, are still effective for patients with difficult-to-treat depressions. Some psychopharmacologists recommend the combination of MAO inhibitors with TCAs,¹⁴ although the literature for the effectiveness of this combination is weak.

Anticonvulsants are currently in favor, both for the prophylaxis of recurrent affective episodes (mainly manic episodes) and for depressive episodes as well. Valproic acid and carbamazepine are being increasingly used in affective disorders, particularly for patients not responding to more standard antidepressant medications.¹⁵

Electroconvulsive therapy continues to be the most effective of treatments for well-diagnosed major depression.^{16,17} Electroconvulsive therapy should not be thought of only as a last resort for treatment-resistant de-

pressions but rather as a front-line treatment for patients with acute suicidality, for profoundly severe depressions, for depressions with psychotic features, for patients with good response to electroconvulsive therapy in the past, and for patients who cannot tolerate side effects of antidepressant medications.

Maintenance Therapy

Most mood disorders are recurrent and therefore should be viewed as chronic conditions. It is no longer sufficient to focus strictly on the acute phase of the disorder. Treatment should be conceptualized and provided to deal with different phases of the disorder including the acute phase, remission phase and maintenance phase. There is some evidence to suggest that depressive episodes tend to become more severe, autonomous, and potentially refractory to treatment with each subsequent episode.¹⁸ Comprehensive treatment of both the acute and maintenance phases of the illness may mitigate the potential for a worsening course.

The acute phase treatment generally lasts 6 to 8 weeks with pharmacotherapy⁸ and 12 to 16 weeks with psychosocial treatments.¹⁹ The goal of the subsequent phase is to prevent relapse and to induce remission. Adequate pharmacotherapy should be continued for 6 to 12 months subsequent to the resolution of acute symptomatology. This is the period with the greatest likelihood of relapse and it makes clinical sense, particularly if there are no significant side effects, to ensure that this high risk period is covered by adequate pharmacotherapy. There is some emerging evidence that psychosocial treatment should also continue during this phase, particularly family treatment, as there may be a tendency for family functioning to worsen during second half of the recovery year.²⁰ For patients without a high risk for recurrence (patients with a first episode of depression or patients with infrequent depressions), a gradual tapering of the antidepressant medication can be undertaken during the 6 to 12 month period.

Maintenance therapy past the 12 month post-episode period should be

considered for patients at high risk for recurrence. These patients include those with more than three previous episodes of depression, those who have had depressive episodes within the previous 2 to 3 years, those with a strong family history of depressions, and those with comorbid conditions that predispose them to ongoing depressions. Evidence from the Pittsburgh Maintenance Therapy Studies²¹ indicates that maintenance therapy should consist of full dose antidepressants similar to those that were successful in inducing remissions during the acute episode. Maintenance therapy for high-risk patients should be continued for at least 3 to 5 years and perhaps beyond. The combination of psychosocial treatments with pharmacotherapy may prolong periods of well-being between recurrent episodes of depression.²²

Psychosocial Treatment

Psychosocial treatments have been used to treat depression since the time of Hippocrates, who prescribed tranquility, sobriety, nutrition and sexual abstinence as a treatment for melancholia.²³ In the 20th century, Freud wrote about the relationship between psychosocial factors and the development of depression, formulating psychotherapeutic approaches to treat depressive disorders.²⁴ Despite this long history of psychosocial approaches, the effectiveness of psychosocial treatments has only been empirically documented in the past 15 years.

Treatment of the Acute Episode

While early empirical studies did not provide strong support for the efficacy of psychosocial approaches in treating the acute episode,^{25,26} more recent studies have demonstrated that psychotherapies can be effective treatments for depressive disorders.²⁷ Numerous studies have demonstrated that psychotherapy can be effective for outpatients with major depression.²⁸ Psychosocial treatments typically have produced response rates significantly better than no treatment, waiting list, or placebo control groups.^{29,30} Other studies have compared psychosocial

treatments to pharmacological therapies.³¹⁻³⁶ In general, these studies have found that psychotherapy alone is at least as effective as medication alone in the treatment of outpatient depression. While some authors have argued that the psychosocial treatments have produced better treatment response,³⁷ others have pointed out that none of these comparative studies have used the type of optimal pharmacological treatment described previously in this paper.^{38,39}

All the studies discussed above have been conducted on outpatients with mild-moderate levels of depression. No controlled study has investigated the effectiveness of psychosocial treatments alone in the treatment of more severe depression. However, recent case reports by Thase et al^{40,41} have described positive results using cognitive therapy in the treatment of: a) moderate-severe outpatients who meet criteria for endogenous depression;⁴¹ and b) severely depressed inpatients.⁴⁰ While these reports suggest that psychosocial treatments alone may be effective for some more severely depressed patients, these studies are not controlled trials. Without further evidence, these authors recommend against use of psychotherapy alone for severely depressed patients unless the patient cannot take antidepressant medication safely or refuses pharmacological treatment.⁴²

Maintenance Treatments

Notably fewer studies have investigated the maintenance effects of psychosocial treatments for depressed patients. Several studies have investigated the long-term outcome of patients treated with psychotherapies.⁴³⁻⁴⁶ Generally, these studies have found that patients treated with psychotherapies had lower relapse and recurrence rates than patients treated with short-term antidepressant medication. However, as noted above, current optimal pharmacological treatment of depression involves continuation of medication beyond the recovery from the acute episode. To date, only one study has compared the efficacy of maintenance psychotherapy with maintenance pharmacotherapy.^{21,22} In this study, maintenance individual psycho-

therapy was found to provide significantly lower relapse rates than placebo plus clinical management. However, the effectiveness of this maintenance psychosocial treatment was not as strong as that of maintenance antidepressant medication—although these conditions were not statistically different.

What Are These Effective Psychosocial Treatments?

There are probably hundreds of different types of psychosocial treatments applied to depression, but only a few have been demonstrated to be effective. Most psychosocial treatments have not been rigorously studied, including some of the more commonly used psychotherapies (ie, psychodynamic, gestalt, "eclectic"). While many clinicians assume that a particular type of psychotherapy is useful for depressed patients, without data it is impossible to determine if these treatments are effective. Imagine the Federal Drug Administration approving a new compound to treat major depression without empirical data concerning its efficacy. Yet this is the case with many, if not most, of the psychotherapies that are used in clinical practice to treat depression.

Reasonable therapeutic trials of antidepressants should be in the range of 4 to 6 weeks at therapeutic doses before concluding that they are not effective for a given patient.

The psychosocial treatments found to be effective treatments for major depression consist of individual and marital/family therapies developed in the last 20 years. Effective individual therapies include: cognitive therapy,⁴⁷ interpersonal psychotherapy,⁴⁸ social skills training,⁴⁹ and behavioral psychotherapy.⁵⁰⁻⁵² Marital/family treatments found to be efficacious include: behavioral marital therapy,⁵³ inpatient family intervention,⁵⁴ and problem-centered systems therapy of the family.⁵⁵

While these psychosocial treat-

ments differ in their underlying theoretical rationale and the content of the major treatment focus, they all share a number of core structural components. Since all of these treatments produce similar rates of treatment response, it may be that these common, "nonspecific" characteristics of these therapies are more important than the specific content. The following set of seven factors describes these core commonalities of effective psychosocial treatments for depression (see Table 4).

1. Time-limited. All of these treatments are time-limited and relatively short-term. Typically, these therapies consist of weekly sessions for 12 to 24 weeks. The explicit time-limited nature of treatment is hypothesized to focus both the patient's and therapist's energies and provide greater motivation for rapid behavior change.

2. Explicit rationale for treatment. All of these psychotherapies offer their patients an explicit rationale for the treatment approach. While these rationales differ in their content from cognitive ("the way you think influences your mood") to interpersonal ("The quality of your relationships with others affects your depression") to behavioral ("You can control your depression by increasing the quality and quantity of pleasant activities you engage in"), all of these psychotherapies present the patient with a well-formulated and coherent rationale for the procedures of treatment incorporating the idea that depression is potentially controllable by the patient. Presentation and explication of the rationale for treatment is a major initial goal of all of these treatments.

3. Therapist is active and directive. Therapists in all effective psychosocial treatments take an active stance during treatment. It is the therapist's responsibility to lead and direct the therapy session. The developers of these psychotherapies contend that this type of therapist behavior is necessary to overcome the lack of energy, passivity and helplessness that characterizes depressed patients.

4. Focus on current problems. As opposed to traditional dynamic psychotherapy, current psychosocial treatments for depression focus specifically on problems that the patient is cur-

rently experiencing. Childhood or other experience may be explored, but only when they directly affect the patient's current issues and then only briefly.

5. Emphasis on changing current behavior. Consistent with the focus on current problems, effective treatments for depression focus on changing patients' current behavior. This emphasis serves at least two purposes. First, changing patients' current behavior produces objective improvements in their situation that affect their depression. Second, these changes reinforce the sense of personal control and efficacy consistent with the rationale for treatment.

6. Self-monitoring of change and progress. Since a common symptom of depression is the tendency to perceive events negatively, most depressed patients tend to minimize treatment gains. Most psychosocial treatments for depression guard against this tendency by teaching patients to monitor their own behavior and mood. Again, this strategy serves two purposes. First, it counters depressed patients' tendency to minimize treatment gains, and, second, it reinforces the relationship described in the rationale presented to patients between behavior and mood.

7. Regular "homework" assignments. Most effective psychosocial treatments for depression do not rely solely on activity in the therapy session itself to produce change. Instead, the therapist typically assigns between-session tasks or "homework" to be completed by the patient. This "homework" extends to the "lessons" of treatment beyond the therapy itself and provides patients with a clearer sense of the applicability of the treatment to their real-life problems.

Combination Treatment

Thirty years ago, a major concern in psychiatry was whether drugs could be integrated successfully into the psychotherapeutic treatment of depressed patients.⁵⁶ This concern coincided with the dominance of psychoanalysis as the central therapeutic philosophy and treatment of choice at this time. Further experience with pharmacotherapy and additional research data made

clear that adding drugs did not produce significant deterioration in psychotherapy. Today, the pendulum appears to have swung in the opposite direction and biological therapies are the dominant treatment modality in psychiatry. With the development of new and perhaps better pharmacological treatments for depression, the current question for many psychiatrists is whether to bother integrating psychotherapy with pharmacological treatment. Despite this current emphasis on biology, we believe that the reasons for combining psychosocial treatments with pharmacological treatments today are more compelling than ever. In the following sections, we will discuss the theoretical, clinical and empirical advantages for combining therapies in the treatment of depression.

Theoretical Reasons for Combined Treatment for Depression

Current theories in medicine reflect a "biopsychosocial" model of illness,⁵⁷ which assumes that all diseases have biological, psychological and social factors influencing disease development and progression. For example, risk factors for coronary heart disease include genetic (family history), psychological (emotional style, personality), behavioral (smoking, eating habits), and social (life stress, marital dysfunction) variables. Similarly, many recent theories concerning depression also include biological, psychosocial and social variables.⁵⁸⁻⁶⁰

Supporting this biopsychosocial approach is the increasing research evidence that biological, psychological and social variables influence each other in an interactive fashion. While a review of this research is beyond the scope of the current paper, several examples will highlight the implications of this expanding literature. Research on animals has suggested that a depression analogue (learned helplessness) can be induced by specific environmental events (exposure to uncontrollable negative reinforcement).⁶¹ The resulting "depression" has biological (decreased norepinephrine), psychological (helplessness, failure to

initiate adaptive behavior) and social (social withdrawal) consequences and can be "treated" by both "psychotherapy" (forced re-learning) or medication. Other examples of the mutual influence of biological and psychosocial factors include research suggesting immune functioning is impaired by chronic stress⁶² and medications can change interpersonal perceptions.⁵⁹

In summary, current theory and research in medicine in general, and in depression specifically, suggest that biological, psychological and social factors are mutually interactive and can influence the development and course of the disorder.

Possible Negative Effects of Combining Treatments

Numerous authors have described potential negative effects of using drugs and psychotherapy.^{42,56} Possible negative effects include: 1) drugs interfering with psychotherapy by; a) focusing on symptoms rather than underlying issues, b) providing symptom relief thereby decreasing the patient's motivation, or c) increasing "magical" reliance on the therapist and fostering dependency, or 2) psychotherapy interfering with medication treatment by a) increasing anxiety that may lead to noncompliance, or b) patients acting out transference issues via medication noncompliance.

Several studies and reviews have explored the evidence for the occurrence of these potential negative interactions of drugs and psychotherapy. Uniformly, no evidence has been found for any negative effects of combining treatment.^{56,63,64} Thus, it appears that concerns about negative interactions when combining treatments are unfounded.

Possible Positive Effects of Combining Treatments

The possible positive effects of combined treatment include: 1) medications' increasing the effectiveness of psychotherapy by making the patient more accessible through decreasing symptoms that may impede the patient's ability to profit from psychotherapy (concentration, motivation,

energy, anxiety); 2) psychotherapy enhancing compliance with medication regime; 3) drugs and psychosocial treatments effecting different types of symptoms early in treatment which may produce faster overall treatment response (eg, drugs effect vegetative symptoms while psychotherapy may focus on decreasing hopelessness and helplessness); and 4) psychosocial treatments, particularly family interventions may change the patient's environment so as to decrease the amount of stress and disruption for the patient.

Evidence for the Effectiveness of Combined Treatment

A number of studies have investigated the efficacy of combining biological and psychosocial treatments for depression for depressed outpatients. Overall, these studies indicate that combined pharmacotherapy and psychotherapy produces "slightly superior" and somewhat faster treatment responses than either treatment alone.⁶⁵ Studies have not found any symptom specificity to the different types of treatment.

While these results do suggest that combined treatments are superior, the relatively small advantage for combined treatments is puzzling. However, there are several characteristics of these studies that reduce the likelihood of finding strong differences between combined treatment and monotherapy.⁴² First, the requirements of research protocols may result in treatment combinations that are less than optimal from a clinical perspective. Fixed dosages of medications and psychotherapies are usually specified and the interaction between the psychopharmacologist and psychotherapist may be limited.⁶⁶ Perhaps more important, these studies have used relatively homogenous samples of mild-moderately depressed outpatients. These less severe and single-problem patients are more likely to respond to any treatment, resulting in high rates of response in all treatment conditions. This "ceiling effect"⁶⁷ makes it difficult to demonstrate any additive effects of combined treatments without very large sample sizes.

For these reasons, one might hypothesize that more consistent effects

for the advantages of combined treatment would be found in studies of more severe, chronic and multi-problem depressed patients who are more difficult to treat and less likely to respond. Despite the few studies that have investigated the effectiveness of combined treatment for more seriously disturbed depressed patients, these studies have consistently reported significant advantages for combined treatment. The results of studies conducted by our research group^{68,69} and others⁷⁰ have documented that adding individual psychotherapy to pharmacotherapy produces significantly better treatment outcome for depressed inpatients. Similar results have been reported for marital and family interventions.⁷¹ These results strongly suggest that combining pharmacological and psychosocial interventions produces maximum treatment response for more severely depressed patients.

Indications for Combination Treatments.

There are no well-established criteria to guide which particular combination of treatments are most appropriate for an individual patient. Our research group is currently studying these issues. Until more definitive data becomes available, however, we have to rely on data interpolated from other studies and clinical common sense.

There are a variety of ways in which one can approach the question of indications for combination treatments. One option is to provide all treatments for all patients. In this case, any patient with a depressive illness would be treated with a combination of psychotherapy, pharmacotherapy and family therapy. This would ensure, at the least, that those patients who really could benefit from combined treatments would receive optimum care. Providing all treatments to all patients is not only an expensive proposition, however, but may actually harm some patients by potentially provoking areas in their lives that are not problematic or are in functional equilibrium.

An alternate approach is to provide sequential treatment trials. In this case, the therapist starts with one treatment modality, for instance pharmacotherapy, and if this, by itself, does not

work after a reasonable amount of time, the therapist adds in the next treatment, for instance psychotherapy and finally family therapy if needed. This approach is problematic because of the excessive amount of time demanded for treatment trials, uncertainty about which treatment approach to begin with, and which treatment is really effective.

The third option and the one that we favor is to try to determine which combination of treatments is most appropriate for a given patient and then to provide that combination from the beginning. One way to determine the best combination of treatments is to undertake a comprehensive assessment of the psychological, biological and social aspects of each patient's current presentation and life situation. Biological assessment should include examination for the presence of concurrent medical illnesses, a family history of affective disorders with particular reference to the response of other family members to a particular class of antidepressants, and most importantly the presence of neurovegetative signs and symptoms. Psychological assessment should include an evaluation of current conflicts, dysfunctional attitudes, personality styles and the meaning of the illness for the patient. Social assessment should include evaluation of current life stresses, availability of social supports, and, most importantly, quality of family functioning.

We prefer to use lithium augmentation when there is non-response to adequate therapeutic doses over a sufficiently long period of treatment.

The presence of neurovegetative signs and symptoms, a strong family history of affective disorders, and evidence to suggest that antidepressants have been useful in the past for the patient or other family members are strong indicators for antidepressant therapy. Similarly, the presence of significant intrapsychic conflicts, dysfunctional attitudes and ongoing personality problems are indicators that psychological treatment is going to be

necessary to cause a satisfactory remission. Finally, the presence of ongoing family dysfunction, significant life stresses and inadequate social supports provides strong indication for social interventions, particularly with family therapy.

Not all patients have problems in all of these domains. It is the clinician's responsibility to provide a thorough enough assessment to be able to determine which areas of the patients' lives are most problematic and to match the treatments most likely to address problematic areas. Conversely, the absence of significant problems in any one of these domains would suggest that it is not necessary for a particular treatment modality to be included, allowing a streamlined and more cost-effective way of helping resolve the depressive episode.

Allocating Roles in Combination Treatments

There is no firm prescription for who should be providing the variety of treatments available. Clearly, pharmacotherapy can only be supervised by psychiatrists, although nurse practitioners are playing an increasing role in this area. Who should provide psychotherapy? Who should provide the family therapy? Again, a number of approaches are possible.

Different therapists can carry out the different treatment modalities. This may be advantageous in that presumably therapists providing a particular therapy are likely to become more experienced and effective with it. The disadvantage is a potential lack of coordination, a risk that therapists will not only move and diverge in direction, but may contradict each other or allow overlapping areas to fall between the cracks. Furthermore, therapists experienced and skilled in one therapy modality may be more likely to provide only that therapy to their patients, regardless of need.

An alternate approach would be for the same therapist to provide all the treatment modalities. Only the psychiatrist is in the position of being able to do this given the mental health care delivery system as currently organized. The psychiatrist should be able to provide pharmacotherapy, individual psy-

chotherapy and family therapy as needed. The clear advantage of this approach is that there is an integration of the treatment, a consistent and comprehensive overview and much less likelihood of diversion from the patients' central problems. However, there are disadvantages as well. First, there are very few psychiatrists who are adequately trained to be able to provide the kind of comprehensive treatment approach outlined above. Most psychiatrists receive excellent training in pharmacotherapy, variable degrees of training in individual psychotherapy, and usually very little training in family therapy. It is also increasingly unlikely that third-party payers will reimburse psychiatrists to provide psychotherapy and/or family therapy under the current mental health care reimbursement system when this can be delivered more cheaply and probably as effectively by less costly mental health care professionals.

Electroconvulsive therapy continues to be the most effective of treatments for well diagnosed major depression.

The solution that seems most appropriate at this time is to minimize, at least, the number of therapists involved with a given patient. For those patients with significant biological components to their major depression, a psychiatrist should be involved. The psychiatrist should develop a close working alliance with a small, consistent core group of psychologists, social workers and nurses. This core group of mental health providers needs to become very familiar and comfortable with each other's approaches to decrease the likelihood of providing conflicting information and guidance to their shared patients. Ideally, there should be regular on-going meetings between these mental health professionals to grow together and make sure that their evolving views of psychiatric illnesses continue to be shared. It is also important for patients and families to know that therapists involved in their care communicate regularly with each other. This not only reinforces their sense of security and

confidence in the treatment team but also minimizes the likelihood of splitting and redundancy.

Conclusions

There are many treatment options for depressive disorders including pharmacotherapy, psychotherapy and family therapy. Most clinicians tend to prefer one treatment over others usually based on their theoretical orientation and clinical training. There is mounting evidence, however, that combining pharmacological and psychosocial treatments is likely to be most effective especially for severe depressions.

Pharmacotherapy, by resolving neurovegetative symptoms, may not only provide physical relief but may also make the patient more accessible to psychosocial treatments. Psychotherapy, in turn, may facilitate patients' acceptance of their illness, increase medication compliance and reduce feelings of hopelessness and helplessness. Family interventions can stabilize patients' home environments and increase the availability of social supports, factors known to influence the course of the depressive illness.

The field of psychiatry is mature enough to avoid excessive identification with either biological or psychosocial approaches. Psychiatry is in a unique position among medical specialties to provide a conceptual and clinical paradigm that calls for the integration or combination of biopsychosocial treatments particularly for chronic, remitting and relapsing illnesses.

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Neuropsychiatric Aspects Of Depression

Stephen Salloway, MD, MS
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Depression regularly associated with neurological disorders that cause structural abnormalities in the brain can provide important clues for understanding the localization and pathophysiology of depression.

The biological basis of depression remains uncertain. Depression regularly associated with neurological disorders that cause structural abnormalities in the brain can provide important clues for understanding the localization and pathophysiology of depression. This article will review some features of depression in neurological patients and discuss clinico-pathological correlations and treatment strategies. The article by Dr Goldberg in this issue addresses the topic of depression in the context of more broadly defined medical conditions. After providing a brief neuropsychiatric view of the brain, this article will discuss: 1) depression related to cortical lesions such as stroke, head trauma and epilepsy; 2) depression caused by subcortical brain diseases such as Parkinson's disease, Huntington's disease, HIV encephalitis and small vessel multi-infarct states; and 3) neurological mimics of depression.

Neuropsychiatric View Of the Brain

Figure 1 depicts a neuropsychiatric view of the brain, included to serve as a rough guide to the structures to be discussed in this report. The monoamines serotonin, dopamine and norepinephrine along with acetylcholine are key neurotransmitters modulating mood, anxiety and memory in the brain. Their primary cell bodies are in the upper brainstem and the base of the forebrain. Neurons in the dorsal raphe

(serotonin), locus ceruleus (norepinephrine), substantia nigra and ventral tegmental area (dopamine) and Nucleus Basalis of Meynert (acetylcholine) innervate the caudate and putamen in the basal ganglia and form inter-connecting pathways that supply the hippocampus and amygdala in the medial temporal lobe and the dorsolateral, orbitomedial and anterior cingulate areas in the prefrontal lobe. The internal segment of the globus pallidus and the dorsomedial and anterior nuclei of the thalamus provide important relay neurons to these behaviorally rich circuits.¹ Lesions involving these pathways can produce many of the symptoms seen in idiopathic psychiatric illness. Careful lesion analysis in neuropsychiatry can yield new insights into the behavioral organization of the subcortex, limbic system and frontal lobe.

Secondary Depression—Cortical Disease

Focal Lesions—Stroke/Tumors/Trauma: A possible association between focal neurological lesions and disorders of mood was first described by Hughlings Jackson over a century ago when he described an association between the aura of fear and the presence of a left-sided temporal epileptic focus.² In 1929, Goldstein described patients who became anxious, depressed, labile and irritable following a left hemisphere cerebrovascular accident. He coined the term "catastrophic reaction" to describe these behavioral changes and considered that they represented the patients' frustration with their insurmountable speech and physical impairments. Goldstein speculated that the patients' behavior represented an understandable, but maladaptive, response to a major life stressor rather than a manifestation of an "affective dysregulation" secondary

to the focal neurological insult.³ The relative contribution of exogenous factors (ie, the stress of a disabling stroke) and endogenous factors (ie, the disruption of neural systems regulating mood) in producing affective disorders following cerebrovascular accidents continues to be an area of controversy. This debate exemplifies the complexities that challenge neuropsychiatrists in their attempt to understand the neural systems underlying complex human behaviors. However, cerebrovascular disease has provided a model capable of possibly answering some of these daunting questions.

Although there continue to be conflicting reports, the current data strongly supports an association between left frontal cortical and subcortical focal pathology and the development of a post-stroke depression (PSD).⁴ It has been estimated that almost a quarter of all patients will develop a major depressive disorder following a left hemisphere stroke. Patients with a lesion in the region of the left frontal pole or the left head of caudate are particularly likely to develop a PSD⁴ (see Figure 2A). The presence of pre-existent significant subcortical atrophy or previous head trauma appears

ABBREVIATIONS USED

AZT: Azidothymidine
CSF: Cerebrospinal fluid
DDI: Didanosine
DSM: Diagnostic and Statistical Manual
ECT: Electroconvulsive therapy
HD: Huntington's disease
MOAI: Monamine oxidase inhibitor
MRI: Magnetic resonance imaging
PD: Parkinson's disease
PET: Positron emission tomography
PSD: Post-stroke depression

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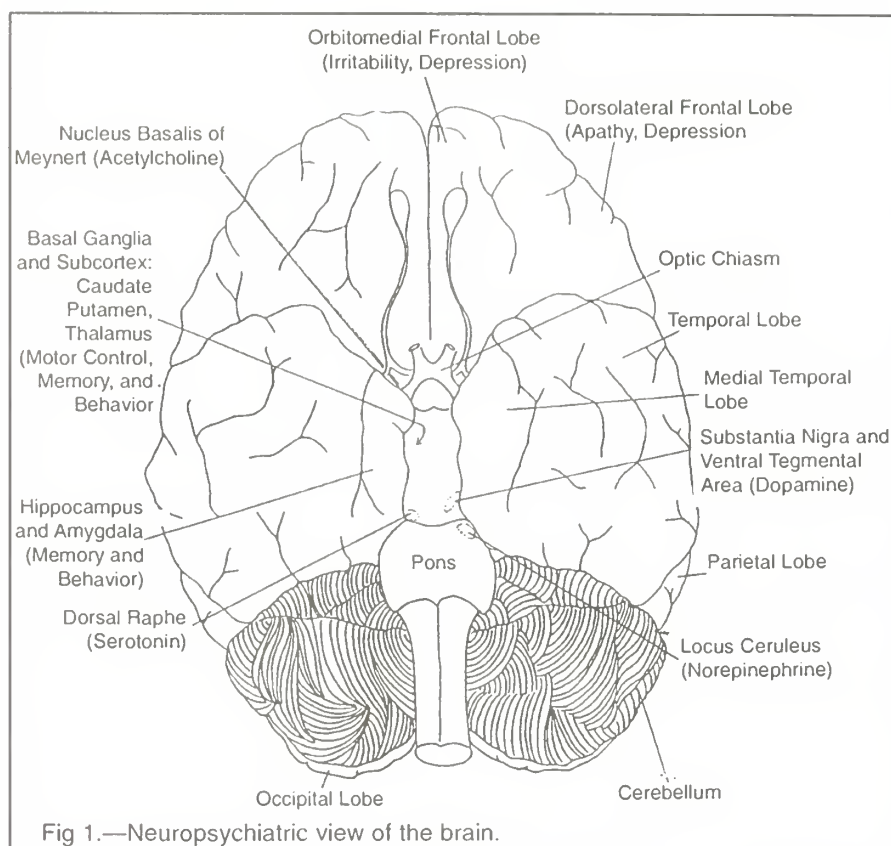


Fig 1.—Neuropsychiatric view of the brain.

to increase the likelihood of developing a PSD. This “secondary” depression usually has its onset within the first year post-stroke and has symptoms that are indistinguishable from a functional major depression. Although current longitudinal data are limited, it appears that the PSD usually resolves within 2 years.⁵ It is interesting to note that the PSD following a cortical rather than a subcortical lesion is more likely to manifest features of anxiety.⁴ The pathogenesis of PSD following left frontal lesions is postulated to result from the selective disruption of noradrenergic fibers as they ascend to the cortex via the left frontal pole.⁴

Further evidence that left frontal lesions cause depression comes from a recent study that reports patients with traumatic brain injury involving left frontal regions are most likely to become depressed.⁶ PET studies also have demonstrated decreased metabolism in the dorsolateral frontal lobe in idiopathic depression that normalizes after the depression is treated.⁷

Patients with right hemisphere strokes may also develop PSD. However, unlike left-sided lesions, a depression is most likely to follow a stroke involving the right parietal lobe.⁸ Current evidence suggests that

individuals with a positive personal or family history of depression are most likely to develop a depression following right posterior lesions. As one would expect, PSD inevitably results in increased functional impairment and prolonged, frequently less effective, rehabilitation.⁹

Less commonly, mania also may occur following focal neurological insult such as a cerebrovascular accident. Contrary to PSD, mania is most likely to follow lesions of the right frontal lobe. Current data suggests that for mania to result, lesions must involve paralimbic structures (ie, the orbitofrontal and basotemporal cortex). Mania following right-sided subcortical strokes involving the thalamus and head of the caudate have also been reported. The pathogenesis of these secondary manias remains speculative but may involve the disruption of limbic and paralimbic pathways.^{4,10}

Both the tricyclic antidepressant nortriptyline and electroconvulsive therapy are effective in treating post-stroke depression.¹⁰⁻¹² The benign side-effect profile of the selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline) makes these agents attractive in patients with cerebrovascular disease but their efficacy in “post-stroke” depression remains unproven. Lowered doses may be indicated because of increased susceptibility to side-effects after a brain injury.

Epilepsy: Depression is frequent among persons suffering from epilepsy. Mendez reported that more than half of all epileptics seen in an outpatient neurology clinic listed depression as a symptom compared to one-third of other neurological patients

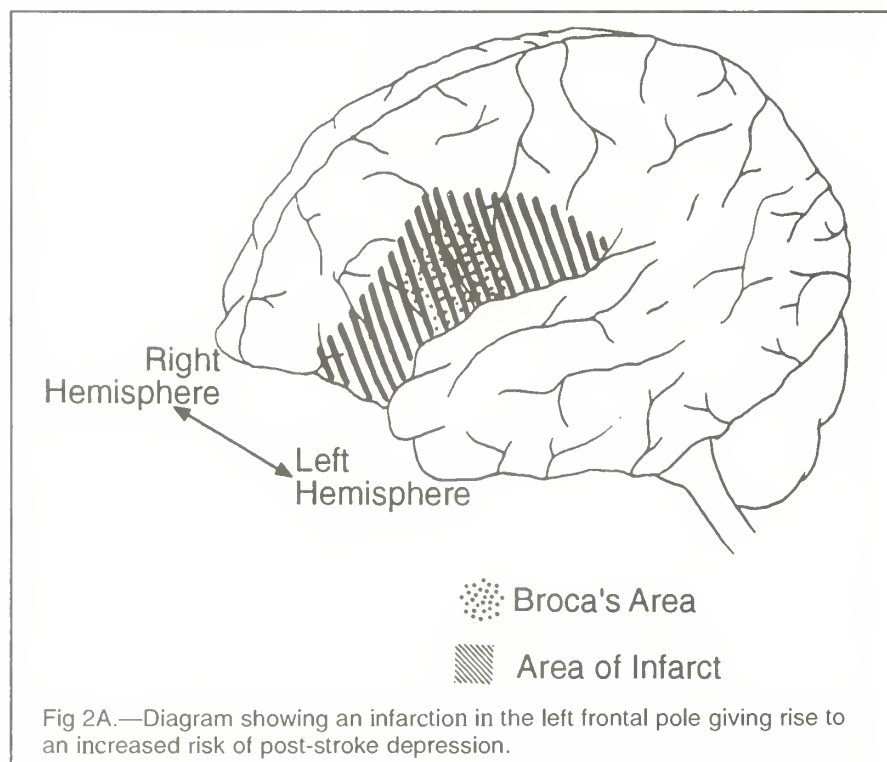


Fig 2A.—Diagram showing an infarction in the left frontal pole giving rise to an increased risk of post-stroke depression.

with equal disability.¹³ He also reported that one-third of epileptics had a prior history of suicide attempts compared to 7% of matched "neurological patients."¹³ As with cerebrovascular disease, it has been difficult to ascertain whether the person with epilepsy becomes depressed as a consequence of the disease process itself or as an understandable response to the psychosocial stressors experienced by the epileptic. Depression may be a manifestation of any phase of the "epileptic cycle" (ie, peri-ictal, postictal or inter-ictal periods). Only the prolonged dysphoria sometimes experienced during the inter-ictal period is capable of meeting *DSM-III-R* criteria for a major depressive disorder. Although by no means conclusive, current data suggest that depression, at least in males, is more likely to be found with left temporal foci and is characterized by more irritability, psychotic features and mood lability than is typical of a primary depressive disorder.¹³⁻¹⁵ Interestingly, several studies have noted a decrease in seizure frequency before the onset of the depressive disorder—a finding consistent with the therapeutic efficacy of electroconvulsive therapy. The pathogenesis of mood change in epilepsy remains uncertain and may involve sustained alterations in neurotransmitters or the kindling of limbic structures subserving the regulation of mood.¹⁶

Data concerning the most effective treatment of the depression associated with epilepsy remains limited. Several studies have reported that maintaining patients on anticonvulsant monotherapy, rather than polytherapy, is likely to improve their mood and cognition. In addition, carbamazepine has demonstrated antidepressant effects while phenytoin, primidone and phenobarbital are more likely to produce dysphoria and cognitive sequelae.^{17,18} Although sodium valproate has documented efficacy as a mood stabilizer, its antidepressant activity requires further clarification.

Secondary Depression—Subcortical Disease

The subcortex consists of white matter tracts connecting the cortical mantle with the basal ganglia nuclei, thalamus and brainstem. Parkinson's

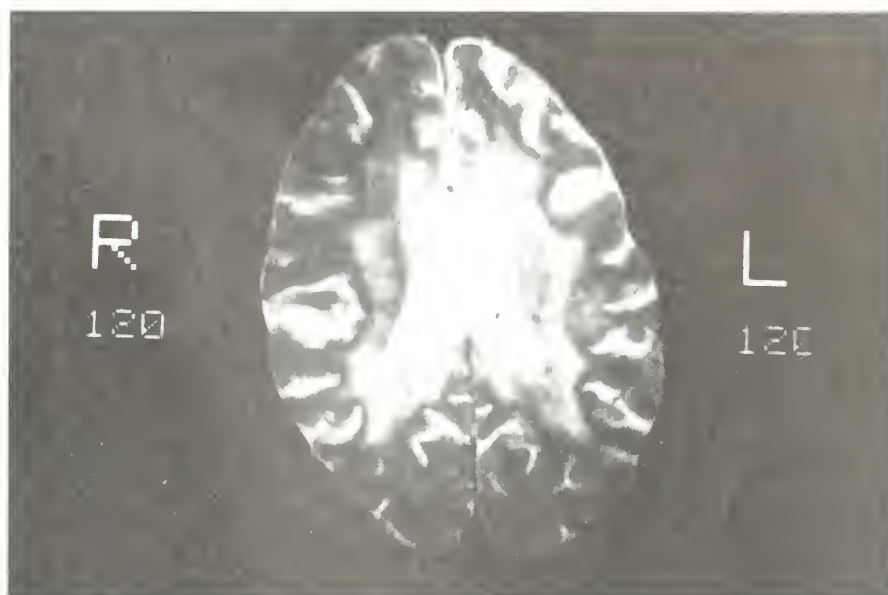


Fig 2B.—CT scan of the brain with contrast in a patient with early Huntington's disease, demonstrating bilateral atrophy of the head of the caudate nucleus and dilatation of the frontal horns. This patient had depression with suicidal ideation and cognitive impairment.

disease, Huntington's disease, HIV encephalitis and multi-infarct states can involve these subcortical structures and cause symptoms of depression. (Extrapyramidal movement disorders will be the subject of an upcoming edition of RHODE ISLAND MEDICINE.)

Depression and Parkinson's Disease

Depression occurs in approximately 40% of patients with Parkinson's

disease (PD). Half meet criteria for a full major depressive disorder and the other half suffer from more chronic smoldering symptoms of depression called dysthymia. The depression associated with PD may precede the onset of motor symptoms and does not appear to be just a reaction to the chronic illness.¹⁹ Interestingly, PD patients may report sadness but usually do not complain of feelings of guilt or self-reproach. There is also a relatively low suicide rate in depressed

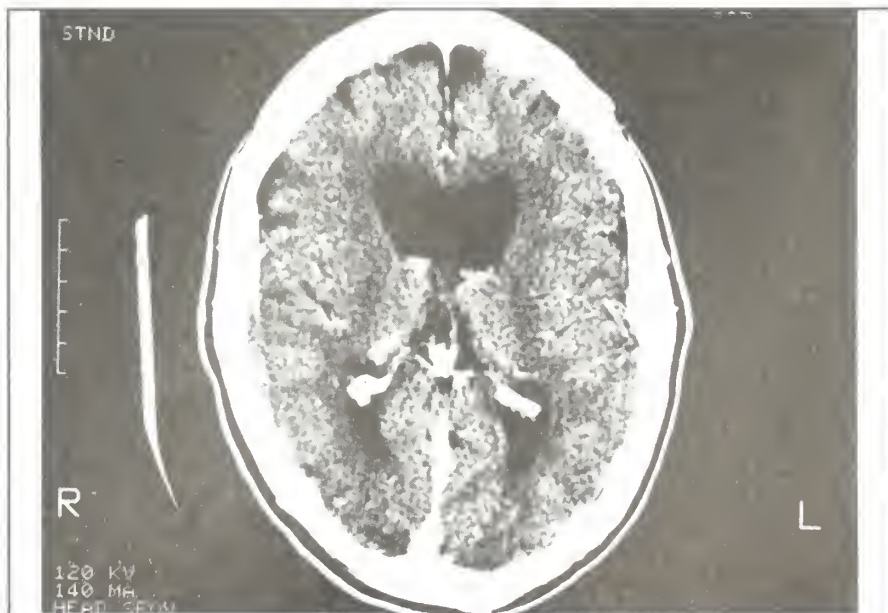


Fig 2C.—T2 weighted axial proton density MRI scan in a 70-year-old man with new onset of psychotic depression. There is intense signal in the periventricular white matter, probably caused by narrowing of subcortical vessels and softening of the white matter.

PD patients. Anxiety may accompany the depressive symptoms or arise as an independent problem.²⁰ PD patients often appear depressed because of the masked facies and psychomotor slowing or apathy due to bradykinesia and bradyphrenia. Clinicians should ask patients directly about their mood state and not assume that the presence of blunted affect reflects an underlying depression.

Pathophysiology of Depression in Parkinson's Disease: A loss of dopaminergic neurons in the substantia nigra of the midbrain causes the classic motor symptoms of PD. There is also a loss of dopaminergic cells in the ventral tegmental area of the midbrain which supply dopamine to the frontal lobe and limbic system. This loss of dopamine probably plays a major role in causing psychomotor slowing, blunted affect and apathy. Dopamine activity normally increases in the frontal lobe during stressful events. The loss of this dopaminergic plasticity may make it more difficult for PD patients to regulate their response to stress.²⁰ Another clue about the role of dopamine in depression is seen in patients with chronic cocaine use. Initially cocaine use produces euphoria by increasing dopamine availability by blocking the reuptake of dopamine into the presynaptic neuron. Chronic use causes the down-regulation of dopamine receptors and depletion of dopamine stores leading to states of severe depression.²¹

Serotonergic, noradrenergic and cholinergic neurons degenerate in PD but not to the same degree as the dopaminergic cell loss. Serotonin plays an important role in the regulation of mood and may contribute to depression in PD. Mayeux demonstrated a low level of the serotonin metabolite 5-HIAA in the CSF of severely depressed PD patients but normal levels in PD patients without depression or with only mild dysthymia.²² McCance²³ induced a severe depressive reaction in a PD patient by depleting his diet of the serotonin precursor tryptophan. The depression was reversed when tryptophan was replaced.

Treatment: Depression in PD should be treated if the symptoms interfere with the patient's daily functioning or cause a significant level of distress. Few controlled trials have

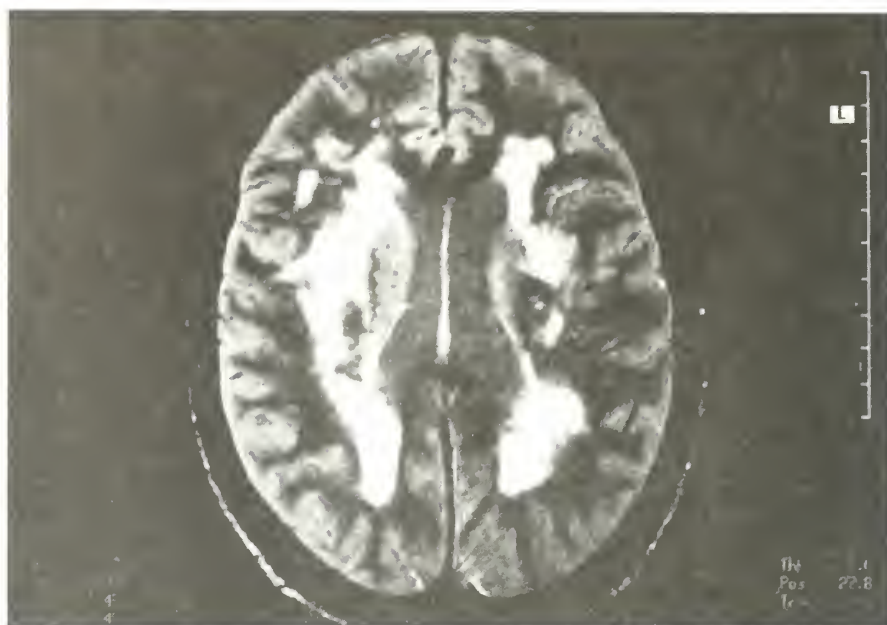


Fig 2D.—T2 weighted proton density MRI scan in a 70-year-old man with new onset of psychotic depression. There is intense signal in the periventricular white matter, probably caused by narrowing of subcortical vessels and softening of the white matter.

been carried out to guide us on which medication to use. PD patients may respond to lower doses of anti-depressants and may not tolerate the standard doses used to treat idiopathic depression. It is important to watch for anticholinergic side-effects such as sedation, confusion, constipation or urinary retention. The activating antidepressants, particularly serotonergic drugs, may cause insomnia, disinhibition, anxiety or irritability and occasionally cause dyskinesia. ECT may effectively treat the depression and transiently improve motor performance.²⁴ PD patients are susceptible to post-ECT delirium.²⁵ Deprenyl is a relatively new monoamine oxidase inhibitor specific for dopamine which has some mild mood enhancing effects at low doses and becomes an antidepressant at higher doses (20 mg/d). Patients on higher doses must be on an MAOI diet.

Huntington's Disease: Huntington's disease (HD) implicates the caudate as a major neurobehavioral center. HD commonly presents as a clinical triad of dyskinesia (chorea), dementia and depression. Approximately 40% of HD patients develop depression. Suicidal acts and ideation are common and often precede the onset of chorea or the diagnosis of HD. The pathological hallmark of HD is marked neuronal cell loss within the

caudate and putamen in the basal ganglia (Figure 2B). Chorea is closely associated with putamen loss and dementia and depression follow cell loss in the caudate. The caudate is connected in a very specific manner to various behavioral regions of the frontal lobe. As one might expect, Mendez⁽²⁶⁾ has shown that strokes in the caudate may produce a clinical constellation of apathy, disinhibition and affective disturbance.

HIV Encephalitis: HIV infection frequently induces a subacute encephalitis that affects the periventricular white matter and basal ganglia nuclei (Figure 2C) and which may lead to the AIDS dementia complex. Patients develop psychomotor retardation, apathy, social withdrawal, sleep disturbance, mood swings and paranoia that may resemble depression. HIV encephalitis is another example of a subcortical process that disrupts fronto-subcortical connections giving rise to symptoms of depression. AZT and DDI can help limit the severity of the psychiatric and cognitive symptoms early in the course. Holmes²⁷ has suggested that low doses of psychostimulants such as methylphenidate and dextroamphetamine may help decrease the apathy, lethargy and psychomotor retardation.

Subcortical Leukoencephalopathy: MRI has allowed better visual-

ization of abnormalities in the subcortical white matter, which are frequently due to narrowing of small penetrating arteries that do not form anastomoses (Figure 2D). Usually multiple vascular risk factors are present. The clinical significance of the subcortical hyperintensities seen on MRI scans in older patients is under active study.²⁸ Many patients develop prominent symptoms of depression, apathy, memory loss and decreased self-care. The white matter disease is thought to cause the cognitive and affective symptoms by interrupting fronto-subcortical behavioral pathways and limbic memory circuits to the subcortex and basal forebrain. Few controlled clinical trials have been carried out to try and slow the natural progression of the small vessel disease. We recommend controlling the vascular risk factors and treating the patient with an antiplatelet agent such as aspirin or ticlopidine. The depressive symptoms may be quite disabling and patients may tolerate standard antidepressant treatment poorly. Coffey et al²⁹ have suggested that ECT may be the most efficacious and best tolerated treatment for depression in the setting of severe leukoencephalopathy.

Neurological Mimics of Depression

Patients with primary neurological disorders may exhibit symptoms that are often misinterpreted as primary mood disorders. Current psychiatric nomenclature is somewhat misleading in its failure to distinguish clearly between disorders of *mood* and disorders of *affect*. In simple terms, affect describes an individual's outward display of his/her internal feeling state while mood describes the individual's sustained feeling state. Although a person's affective display is usually a valid measure of his/her mood state—certain neurological disorders may render this assumption invalid.

The right hemisphere has a dominant role in the perception and expression of affect with an organization for non-verbal behavior (eg, smiling, hand gestures, body language) that mirrors the verbal language system in the left hemisphere. This behavior is referred to as *prosody*—a term that describes the melody, intonations, pauses and

hand and body movement used in embellishing the words used in language. Lesions of the right hemisphere produce abnormalities in the individual's ability to communicate appropriately their own feelings (*expressive dysprosody* or *aprosody*) or to interpret the feeling state of others (*receptive dysprosody* or *aprosody*).³⁰

Patients with an expressive aprosody have reduced hand and body gestures, speak in a monotone and have diminished facial expression. These physical characteristics are frequently misinterpreted by the clinician as indicative of a depressive disorder. Causes of an expressive aprosody include right posterior peri-sylvian strokes, trauma or tumors and non-verbal learning disabilities.³⁰ The *psychomotor retardation* exhibited by patients with Parkinsonism, frontal lobe damage, akinetic mutism and subcortical dementias is often misinterpreted as evidence of depression.

Patients with an expressive aprosody have reduced hand and body gestures, speak in a monotone and have diminished facial expression. These physical characteristics are frequently misinterpreted by the clinician as indicative of a depressive disorder.

Patients with frontal lobe deficits, particularly those involving the orbitofrontal region, frequently display exaggerated affective responses to relatively unimportant "environmental cues." This emotional lability reflects their lack of usual inhibitory emotional tone and is referred to as "*pseudo-bulbar affect*." They may cry or laugh loudly and inappropriately while watching a soap opera on television and are usually embarrassed by their "increased emotional knee jerk." Since the affective display of these patients is driven by environmental cues they may appear either depressed or euphoric depending on the immediate stimulus. This disorder is distinguished from primary mood disorders both by the absence of sustained alterations in mood and the somatic symptoms of a

major depressive disorder. Common causes of pseudo-bulbar affect include cerebrovascular accidents, tumors and trauma involving the orbitofrontal cortex. Currently accepted treatments for pseudobulbar affect include low doses of tricyclic (and possibly serotonergic) antidepressants, l-dopa and amantadine.³¹⁻³³

Cognitive Consequences of Depression

The association between primary depressive disorders and cognitive deficits has been recognized for over a century. In the late nineteenth century, Wernicke coined the term *pseudodementia* to describe the reversible cognitive deficits that are frequently found in depressed patients. The incidence of significant cognitive deficits secondary to depression increases with age and is unusual in young depressed patients. As many as one-third of depressed patients over age 65 will manifest significant cognitive deficits that respond to antidepressant treatment.^{34,35} In older patients the contribution of concomitant neurodegenerative conditions often confounds attempts to define clearly the relative contribution of depression to any cognitive deficits. Definitive statements regarding the presence of a primary dementing process should therefore be deferred until the patient's depression has been adequately treated. Current data suggests that the dementia of depression is not an indicator that the patient will later develop a primary dementing illness.³⁴

Patients with the "dementia of depression" exhibit the "I don't know" syndrome characterized by poor motivation and a generalized "cognitive dilapidation." The patients' failure to energize themselves to answer questions results in global deficits on neuropsychological testing. These deficits are similar to those found in patients with PD. This suggests that similar pathophysiological mechanisms involving subcortical systems are involved in both diseases.^{35,36} As stated above, the cognitive deficits of the "dementia of depression" are entirely reversible upon treatment of the underlying mood disorder.

Depression and Alzheimer's Disease: Depression can also be a com-

mon problem in Alzheimer's disease.³⁷ Depression in Alzheimer's disease frequently is associated with psychotic features such as paranoia. If the depressive symptoms interfere with daily functioning they should be treated. Unlike the treatment of pseudodementia, mood may improve but significant cognitive impairment usually persists. There is evidence that many depressed patients with Alzheimer's dementia can be safely treated with ECT.³⁸

Conclusion

Advances in psychiatric nomenclature and basic neuroscience have, for the first time, provided neuropsychiatrists with the foundations for developing an understanding of the complex neural mechanisms underlying mood and affect. This paper attempts to highlight the neurological antecedents and sequelae to primary and secondary mood disorders. The clinician's heightened awareness of these associations will improve therapeutic efficacy and long-term outcome.

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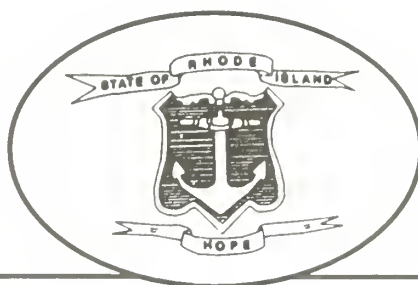
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Anomalous Increase in Reported Deaths, March 1993, Rhode Island

During March 1993, 1090 certificates for deaths occurring in Rhode Island were filed with the Rhode Island Office of Vital Records. This number of certificates was 218, or 25%, above the average number filed during March in the previous 9 years (1984-1992) and 148, or 16%, above the next highest month (942, in January 1985) recorded since the beginning of 1984 (Figure 1). In comparison, the numbers of deaths filed during January, February, April, and May of 1993 were all within the expected ranges for those months, with only January falling substantially below the 9-year average for that month (Table 1). The March increase was first noticed as an increase in obituaries published during March 1993 in the *Providence Journal-Bulletin* and was reported by the paper's science writer, C. Eugene Emery, Jr., on April 7.

To investigate the cause or causes of the sudden increase in deaths in March 1993, death certificate data for that month were analyzed in comparison with data for deaths filed during March of the previous 3 years, 1990-1992. Specifically, the distribution of decedents by age, sex, race, residence (state, city/town), day of death, setting of death (eg, hospital, nursing home), and cause of death were analyzed for significant differences and patterns. In addition, other information on disease and injury trends available to the department were examined, and monthly data on filings were request-

ed from neighboring states.

When March 1993 deaths were compared to March deaths of previous years in terms of age, sex, race, state of residence, and city/town of residence, no statistically significant differences were observed in the distributions. However, the percentage of deaths occurring in nursing homes in March 1993 (26.7%) was significantly higher than the average for March of the previous 3 years (23.3%). Furthermore, the distribution of deaths by cause in March 1993 differed from previous years, with statistically significant declines in the proportions of deaths from cancer and injuries and a statistically significant increase in the proportion of deaths from pneumonia and influenza. The elevation in deaths during March 1993 appears to have occurred evenly throughout the month, with no pattern of exceptionally high numbers of deaths on specific days that might correlate with external factors, such as extreme weather occurrences.

Patterns of cause of death were further examined by comparing the raw numbers of deaths in March 1993 with averages for March of 1990-92. Large increases were seen in deaths from most major chronic diseases, including heart disease (+100), stroke (+23), and chronic obstructive pulmonary diseases (COPD, +20). A large increase was also seen in pneumonia and influenza deaths (+25), and a decrease was observed in injury deaths (-

19), including homicides, suicides, and unintentional injuries (Figure 2).

Information from other sources suggests possible causal factors for the observed increase in deaths. In 1993, reported cases of "flu-like illness" peaked late in the season compared to the previous 3 years, with very few cases reported in January 1993 and with the number of cases reported in March 1993 being over 5 times the average for March during 1990-1992 (Table 2). Also, the overall weather pattern for March 1993 may have represented a health burden, as that month recorded the lowest mean temperature, highest cumulative snowfall, and highest total precipitation of any March in the past 4 years. Finally, the high number of deaths occurring in Rhode Island in that month appears to be an isolated phenomenon, as neither Connecticut nor Massachusetts observed a similar increase in the number of death certificates filed.

In summary, the unusually high number of deaths occurring in Rhode Island during March 1993 was the result of a number of factors, likely including some not revealed in this analysis. The clearest causal factor was the combination of a delayed peak in influenza cases and a long period of unusually severe weather, which together appear to have precipitated the deaths of large numbers of persons with chronic cardiovascular and pulmonary diseases, resulting in an excess of such deaths during the month.

Submitted by Jay S. Buechner, PhD, Office of Health Statistics; Bela Matyas, MD, Division of Disease Prevention and Control; Joseph Aldoriso, Office of Vital Records; and William J. Waters, Jr., PhD, Deputy Director of Health. Health by Numbers is edited by Jay S. Buechner, PhD, and William J. Waters, Jr., PhD.

Table 1.—Number of Certificates Filed for Deaths Occurring in Rhode Island, by Month of Filing (Selected Months), 1984-1992 Average and 1993.

Month	Average, 1984-1992	1993
January	895.0	815
February	812.6	808
March	871.8	1090
April	806.4	853
May	802.8	771

Table 2.—Cases of Flu-Like Illness Reported to the Rhode Island Department of Health, by Month of Diagnosis (Selected Months), 1990-1993.

Year	January	February	March
1990	596	521	326
1991	1342	696	417
1992	501	308	31
1993	86	419	1407

Fig 1.—Frequency Distribution of Number of Death Certificates Filed per Month for Deaths Occurring in Rhode Island, January 1984 - May 1993.

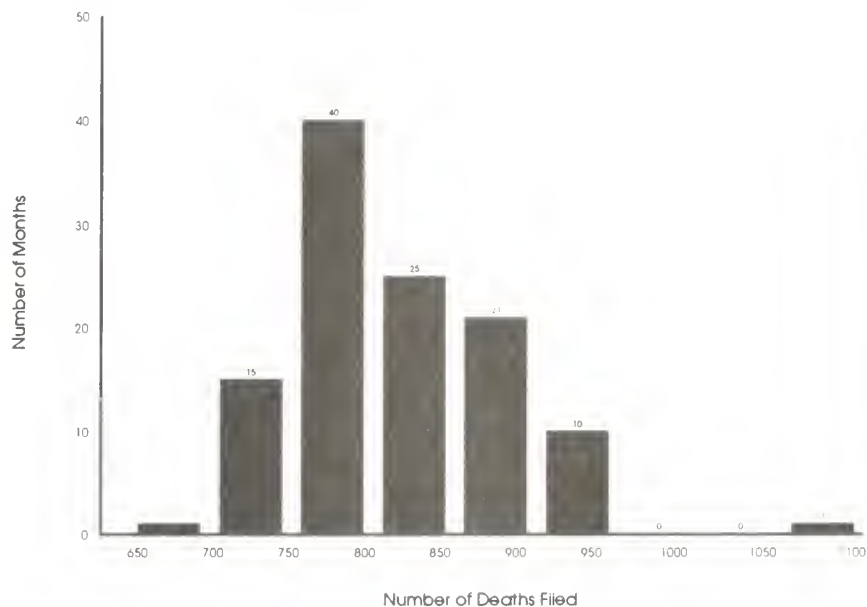
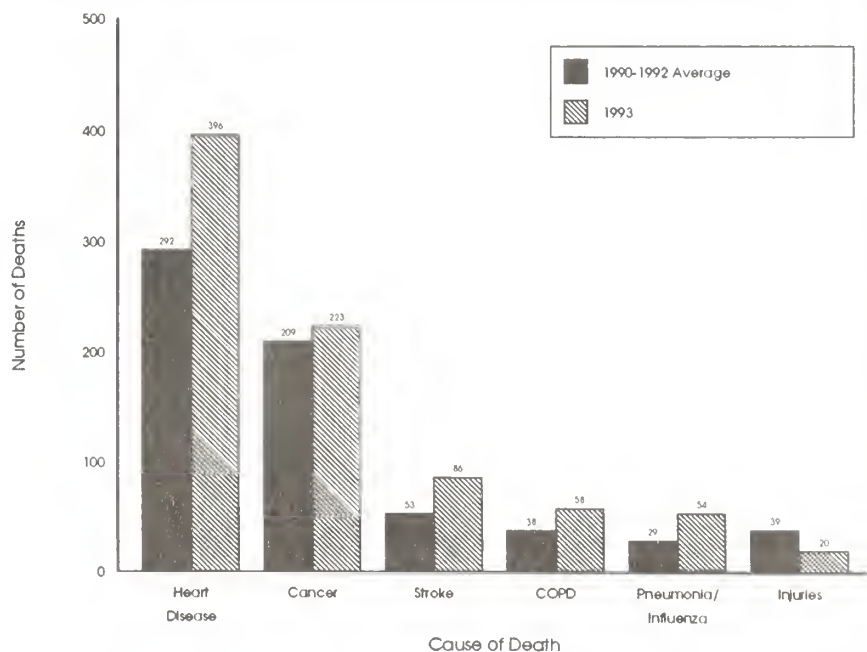
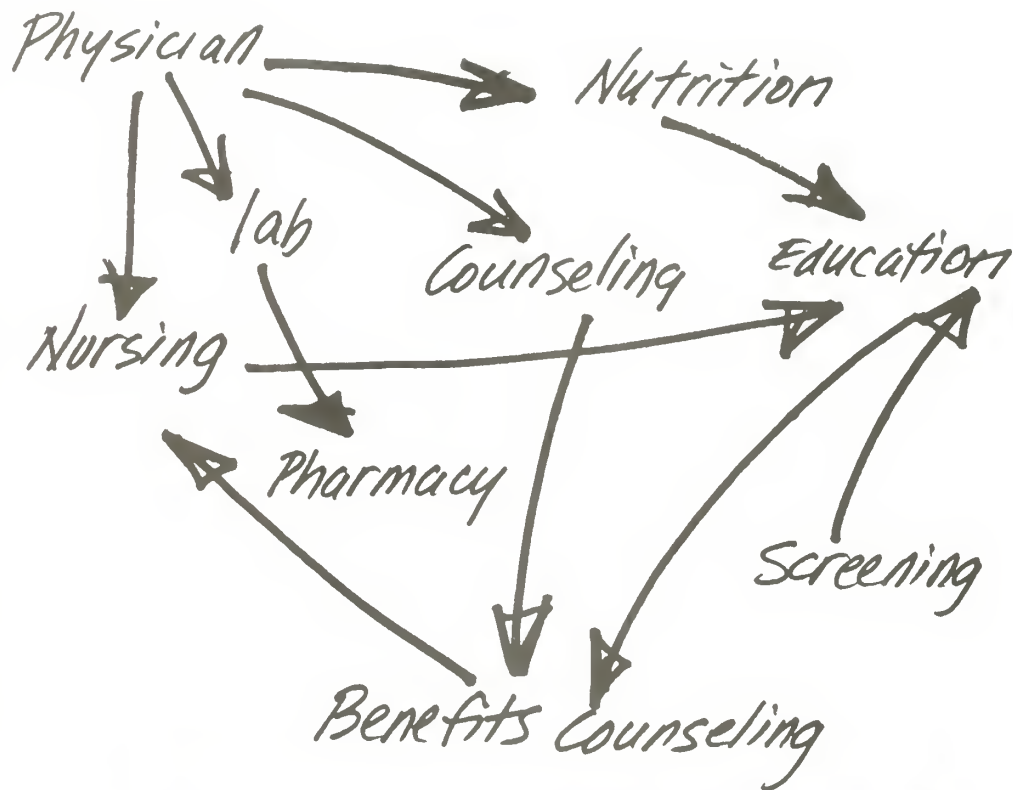


Fig 2.—Number of Deaths Filed in March, by Cause of Death (Six Leading Causes), Rhode Island, 1990-1992 Average and 1993.





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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

90 Years Ago August 1903

Frank E. Peckham, MD, a Providence orthopedic surgeon, writes on his experience with fractures of the neck of the femur. He observes: "There is no more difficult problem in fracture work than the treatment of such a condition in the neck of the femur, whether the patient be young, middle aged or old. If you will examine most every case where such fracture existed, you will find shortening and eversion." The author then describes two cases, in detail, where he institutes a new procedure requiring the use of "a bone peg" to anchor the neck of the femur and to achieve a more solid union at the fracture site. By such procedures, he believes, the lower limb asymmetries and disabilities are substantially diminished. Peckham emphasizes that traction must, however, be applied to the affected leg (to counteract the cephalad movement of the trochanter following a fracture of the femoral neck), marked abduction while the fractured faces are being apposed, and the use of a bone peg to hold the neck of the femur firmly at the correct angle. Rather than a conventional plaster spica, the author advocates the use of a Thomas splint to diminish the likelihood of pressure sores and to permit the periodic cleaning of the skin of the affected leg. The author notes that he adopted these procedures (particularly the use of bone pegs), beginning in August 1900 but did not publish his clinical (and radiographic)

results until the summer of 1903. In the interval, a New York orthopedic surgeon published a virtually identical technique in November 1902, thus apparently establishing priority. The author ends his description with the following statement: "I would advise and urge the bone-peg operation because it is practically a bloodless operation, nothing but skin and fascia being divided. It is too soon to report these (new) cases because it is ultimate results that are desirable but so far everything is favorable and much to be preferred to any method that is known to me."

George W. van Benschoten describes in great detail the causes and prognoses of sudden blindness. He recommends, at all times, "the intelligent use of the ophthalmoscope." The major causes are listed as follows: (1) Embolism of the central retinal artery or thrombosis of the retinal vein. This blindness comes on very suddenly, and is often absolute; it is most often monocular. The ophthalmoscopic picture is quite typical. (2) Apoplexia retinae. (ie, Hemorrhage into the retina and/or vitreous.) This painless condition may be brought about by excessive physical exertion or even maternal labor. (3) Systemic hemorrhage (eg, gastrointestinal, gynecologic, urinary etc) may bring on blindness. (4) Uremia usually causing bilateral blindness. This form of amaurosis is often reversible. (5) Spasm of the retinal vessels or ischemia of the retina. Usually monocular and almost always reversible within hours. (6) Sudden

blindness caused by detachment of the retina. (7) Hysteria. "While complete loss of sight may occur (in this condition) it usually develops gradually with a concentric, progressive narrowing of the field of vision. The great majority of cases occur in women and follow frequently some mental shock. The pupils dilate and contract regularly even in the blind eye." (8) Sudden blindness during the course of acute infectious disease (eg, scarlet fever, malaria, yellow fever, cholera, influenza.) (9) Rare causes, including, disseminated sclerosis, rupture of internal carotid artery aneurysm, post-ictal states, and blinding lights (eg, lightning.)

50 Years Ago August 1943

The lead, and only, paper is by Edwin H. Place, MD, giving the second Charles V. Chapin Oration, speaking on the changing views of contagious diseases. The author begins by emphasizing the critical importance of controlling the carriers of contagion, not necessarily by identifying them as much as by comprehensive programs of mass immunization. With meningococcal infections, though, where no immunization is available, carriers can be of particular significance in understanding the epidemiologic dynamics of local collections of active cases. The natural mortality of the disease at this time (1943) is about 65% according to the author. The paper next addresses the problem of scar-

let fever and the debate regarding which of the strains of hemolytic streptococci are capable of elaborating the toxin causing the skin lesions. The author disparages the older view that contagion is determined by the extent of desquamation - and that when skin shedding ceases, the patient is no longer contagious. In his judgment, isolation, quarantine and other measures have been extensively practiced, but so far as evidence can be secured, are without any effect upon the prevalence of the disease. With each disease considered, the author urges that immunization (if available) must be employed. The discussion finally touches upon newer experiments to determine the merit of such preventive modalities as phenol air spray, ultraviolet sterilization of hospital air, and other barrier technics. No mention whatever of the sulfonamides or of a new agent recently discussed in the British literature called penicillin.

An editorial discusses the terrible tragedy surrounding the Coconut Grove nightclub fire - and how much new knowledge regarding rational care of burn victims has been generated by the Boston physicians working with the victims of that fire.

There are many items within this issue discussing the experiences of Medical Society members who are in military units overseas.

One full-page advertisement, sponsored by Philip Morris cigarettes dem-

onstrates that instillation of a smoke solution from its brand produces only 8 minutes of rabbit conjunctival edema compared with 45 minutes with other cigarette brands. The ad states: "When smokers changed to Philip Morris, every case of irritation of the nose and throat due to smoking cleared completely or definitely improved."

25 Years Ago August 1968

The entire August issue of the Journal is devoted to a symposium on the status of diabetes mellitus. The lead article is a reprint of a pamphlet on the nature of diabetes written by Sylvanus Clapp, MD (1815-1879) an 1836 graduate of Dartmouth medical school, consulting physician to Rhode Island and Butler Hospitals and president of the Rhode Island Medical Society from 1864 to 1866. This privately printed essay begins with a summary of the older perceptions (Galen and Aretus) of diabetes, ascribing the disorder to renal irritation producing excessive urine and much body wasting. Thomas Willis (17th century) described the intensely sweet taste of the diabetic urine. Both he and Sydenham believed that the seat of the disease was in the blood rather than the kidneys. Most every eminent source quoted by Clapp, agreed with either Galen or Willis with regard to the etiology of

the disease. (The initial experiments showing a pancreatic origin to the disease were not to be published for another 3 decades.) The paper discusses clinical characteristics, incidence of the disease (in New England it is a very infrequent disorder), the abnormal metabolism of diabetes as described by Bence Jones and the role of the liver (as studied by Claude Bernard) in glucose metabolism. Therapy, in 1845, consisted of such agents as permanganate of potash, creosote (allegedly retarding glucose formation), opiates, hydrochloric acid, diaphoretics and brandy. Despite the variety of agents used, the author declares that "a fatal outcome is a certainty."

Paul Lacy, MD, describes his recent studies on the structure and functions of the Islets of Langerhans. His investigations include such recent laboratory procedures as electron microscopy, autoradiography and *in vitro* studies.

James B. Field, MD provides clinical clues on the diagnosis of reactive hyperglycemia (Somogyi Effect).

The lead editorial offers the reader a brief but excellent summary of the history of diabetes from the work of Minkowski to the most recent of disclosures. Other editorials touch upon thyrocalcitonin, Wilson's disease, psittacosis (no longer a virus disease), and the resolution by the AMA House of Delegates against discrimination.

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Books:

2. Hollingworth JW. *Local and Systemic Complications of Rheumatoid Arthritis*. Philadelphia, Pa: Saunders; 1968.

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3. Epstein WL. Erythema nodosum. In: Samter M, ed. *Immunological Diseases*, 2nd ed. Boston, Mass.: Little, Brown; 1971;2:944-951.

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose response study. *Clin Cardiol*. 1991;14:146-151

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS)

Pregnancy and Lactation: Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, or electrolyte disorders, or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia: Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SO 31.906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SO 31.945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31.906 and SO 31.945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SO 31.906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids (1 hour prior to PRAVACHOL [pravastatin sodium]), cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a >50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallenian degeneration of retinonucleate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallenian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye-Hardner gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of mutagenicity was observed in vitro, with or without rat liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/– mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo

The following events have been reported with drugs in this class

Skeletal myopathy, rhabdomyolysis

Neurological dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, focal paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting

Reproductive: gynecomastia, loss of libido, erectile dysfunction

Eye: progression of cataracts (lens opacities), ophthalmoplegia

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS)

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required

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pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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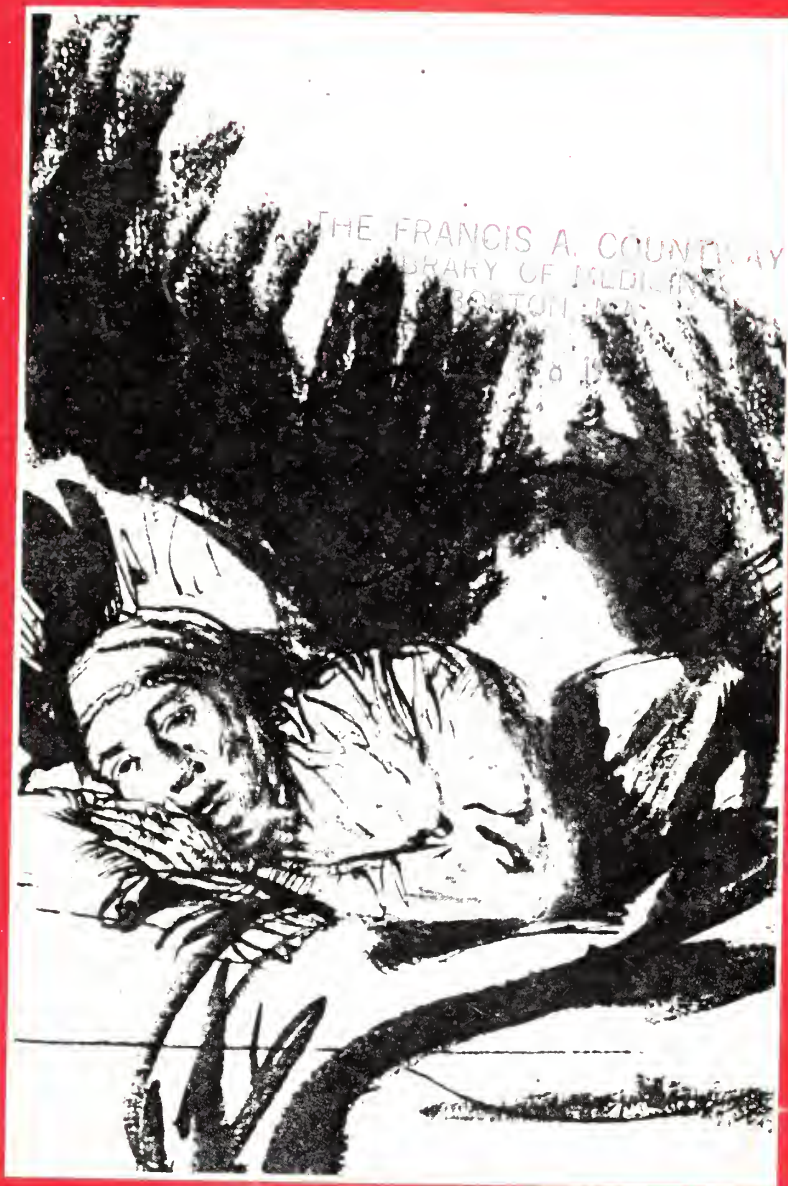


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Rhode Island **MEDICINE**


September 1993

Volume 76, Number 9



AIDS in Rhode Island

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I need a little help
doesn't mean I need
a nursing home."



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Cover: Woman sick in bed; pen and ink sketch by Rembrandt van Rijn.

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Ceramic tiled entry hall with marble floored lavette, 20' x 34' great room with vaulted ceiling, clerestory windows, and Connecticut Stone fireplace. A full window wall view of the Bay.

Bedroom with separate bath in suite, to atrium doors which lead to large private deck overlooking the Bay.

"Fabulous" describes the formal dining room with butler's closet and view to the Bay.

Gourmet chefs would be at home in this larger-than-life custom kitchen, complete with center island sink, rosewood and

laminated cabinets, and top-of-the-line appliances including Jenn-Air cook-top and grill, gas range/oven, electric wall oven, microwave, refrigerators, twin dishwashers, trash compactor, and garbage disposal. The entire kitchen and dining area look directly out to the Bay.

Third bedroom with vaulted cedar ceiling and walls, ceramic tiled floor and private entrance. Third bathroom with shower stall, vanity and laundry closet.

(over)

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SECOND LEVEL . . .

Master bedroom suite consists of bedroom area with glass wall and atrium door leading to private deck overlooking the Bay; a large bathroom with separate toilets and vanities plus a large stall shower and a raised platform corner whirlpool tub; a large closet and exercise area with floor-to-ceiling mirrors complete the master suite.



BASEMENT LEVEL . . .

Unfinished walkout with built-in wine rack and liquor storage, and built-in workbench.

UTILITIES & MECHANICALS . . .

200-amp electrical service, city water, private septic system, gas-fired four-zone forced hot water heating system with computerized setback thermostats. Central air conditioning (three systems). Fifty-gallon gas-fired hot water heater. Central monitored alarm system. Central vacuum.

Oversized three-car garage with 4-burner cooktop hot and cold water, central vacuum and floor drains.



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The Specter of AIDS

This is the second issue of RHODE ISLAND MEDICINE devoted exclusively to AIDS. The papers in both issues (July 1990 and September 1993) have been assembled and edited by Dr Kenneth H. Mayer, director of the Brown University AIDS Program, and Dr Barbara A. DeBuono, director of the Rhode Island Department of Health. They were aided by an increasing number of dedicated and skilled clinicians and research workers who are responding to the peril, both real and imminent, occasioned by AIDS. In 1990, the cumulative number of AIDS cases in Rhode Island hovered about 300. Three years later that number had risen over two-fold.

This issue of RHODE ISLAND MEDICINE provides the readership with a better notion of HIV disease as it affects infants, children and women—as well as adult males. The reader will also find information on the various clinical facilities, field trials and other resources for the physician confronting AIDS in his or her patients.

For information concerning HIV/AIDS counseling or testing, call the Rhode Island Department of Health, AIDS Division: (401) 277-2320

For information concerning AIDS-related clinical trials, call the Brown University AIDS Program Clinical Trials office: (401) 456-AIDS

For general information concerning AIDS, call the Brown University AIDS Program office: (401) 863-1725.

Maladies Unknown to Our Forefathers

AIDS did not burst upon the world community like some avenging pestilence. Rather it began in silence, infiltrating certain high-risk communities, with its human vectors exhibiting neither genital sores, hectic

fevers, nor herald rashes. The HIV pathogen of AIDS propagated quietly by venereal contact or by inadvertent recruitment through transfer of infected biologic fluids to reach, within a decade, its current pandemic dimension. By its lengthy latent interval, HIV infection differed from those communicable diseases that can be lethal within days. Its slow-motion kinetics, however, did not prevent HIV from infecting, and ultimately killing, vast numbers of victims: a torpid plague—but a plague nonetheless.

AIDS is certainly not unique as a totally new and lethal contagion. During the past 6 centuries a number of new infectious scourges ravaged immunologically innocent populations. Preeminent amongst these was the arrival of bubonic plague in Italy (1347); the devastating spread of small pox, brought by the Spaniards to Mexico in 1521, destroying much of the native Meso-American population; the invasion of cholera into southern Russia (and then throughout the Western world) in 1831; and the arrival of syphilis to Spain in 1493, probably carried by sailors who had contracted the disease in the Caribbean islands as well as the Caribbean slave women brought back to Europe.

Most medical historians now reason that syphilis was unknown to the European continent until the crews of Columbus returned with their spirochetal burden. The early spread of syphilis through Spain and France is poorly documented. The new and virulent disease assumed epidemic proportions only when the invading armies of Charles VIII, accompanied by the customary hosts of camp followers, invaded Italy in 1494. The new pestilence, often lethal, was called the Neapolitan sickness by the French and the French sickness (*Mal Franzosa*) by the Italians. Since both opposing armies employed Spanish mercenaries, it seems immaterial which force provided the ini-

tial source of communicable agent. A German ecclesiastic, writing in the beginning years of the 16th century, states: "Providence has seen fit to order things so that nowadays we see maladies unknown to our forefathers springing up around us. It was in the year of Our Lord 1493, or thereabouts, that this pestilential sickness broke out. This happened, not in France, but in the Kingdom of Naples." Oviedo, reporting to the King of Spain, declares: "Your majesty may take it as certain that the *bubas* (ie, syphilis) comes from the Indes, where it is very common amongst the Indians, but not so dangerous in those lands as it is in our own. The first time this sickness was seen in Spain was after Admiral Don Christopher Columbus had discovered the Indes and returned from these lands."

Following its Italian eruption, though, the venereal nature of the illness was inescapable. Benedetto, a Venetian physician in the region, writes: "Through sexual contact, an ailment which is new, or at least unknown to previous doctors, the French sickness, has worked its way in from the West to this spot as I write. The entire body (of the sufferer) is so repulsive to look at and the suffering is so great, especially at night, that this sickness is even more horrifying than incurable leprosy or elephantiasis, and it can be fatal." In 1497, Alexander Benedictus notes: "There appeared a new malady, spread by carnal contact, called the French sickness, and unknown to doctors of antiquity." Even Voltaire, not a physician, observes: "The first fruit gathered by the Spaniards (in the New World) was the pox; it spread more swiftly than Mexican silver."

While the communicable nature of syphilis (or pox) was unmistakably evident, a higher cause for the pestilence was nevertheless sought. To some, "it was God's wrath that allowed this malady to descend upon the human race in

order to curb its lasciviousness and inordinate concupiscence."

In Denmark the new sickness was called *gallica scabies*; in England, Bordeaux sickness; the Spanish physicians, less interested in attribution, chose non-geographic names for the new illness, calling it either *las bubas* (from a Greek word meaning groin) thus identifying the multiple inflammatory swellings and lymphadenopathies about the groin; or *pudendagra* (from the Latin *pudendus* signifying the external genitalia and derived from *pudere*, meaning shame). In Scotland it was named *grandgorre*, a compound word meaning great, festering rot; but it was in France that a name was chosen that prevailed, for a while, over the others. That name was *la grosse verolle* (the great pox, to distinguish it from the small pox).

Numerous 16th century treatises described the clinical progression of the great pox. The visible illness, most observers agreed, began with a painless genital pustule that rapidly ulcerated and festered. This primary lesion, the chancre (a French word originally indicating a cancer or a sore), was typically surrounded by a ring of indurated, inflamed tissue. The primary venereal sore quickly was overshadowed by a disseminated rash, swollen nodes, numerous foul-smelling skin ulcers, fever, hair loss, weight loss and intense bone pains. Within weeks, this was superseded by facial ulcerations, numerous subcutaneous tumors (gummas), distortion of the shape of the limb bones, diarrheas, loss of teeth and sometimes dementia. Death was a common outcome, but there were those who survived and gradually recovered. It would require another few centuries before the delayed neurologic and cardiovascular sequelae of syphilis were etiologically ascribed to the acute illness.

Within 10 years, all of Europe huddled under the shadow of a syphilitic epidemic. And while the pox ultimately affected all social classes, it was initially most visible amongst the migrant, the military and the prostitutes. Decrees attempting to contain the bearers of the great pox flourished. The Edict of Edinburgh, September of 1497, was typical of many; it stated that persons with the great pox (or grandgor) were to be permanently branded on the cheek and then exiled. Within a century, though, the democratic nature of syphilis was revealed as its spread through all social classes, educated and illiterate alike. Syphilis infected both the anonymous and the notorious (eg, Casanova). By the 18th century syphilis

In that dire Season this Disease was bred,
That thus o'er all our tortur'd Limbs is spread ·
Most universal from its Birth it grew,
And none have since escap'd or very few ;
Sent from above to scourge that Vicious Age,
And chiefly by incens'd *Apollo's* Rage,
For which these annual Rites were first ordain'd,
Whereof this firm Tradition is retain'd.

A Shepherd once (distrust not ancient Fame)

Possess these Downs, and *Syphilus* his Name.

A thousand Heifers in these Vales he fed,

A thousand Ews to those fair Rivers led :

For King *Alcithous* he rais'd this stock,

And shaded in the Covert of a Rock,

For now 'twas *Solstice*, and the *Syrian* Star

Increas'd the heat and shot his Beams afar ;

The Fields were burnt to ashes, and the Swain

Repair'd for shade to thickest Woods in vain,

F f f 3

No

was intimately associated, in the words of Bierce, with those who had so earnestly pursued pleasure that they had the misfortune to overtake it.

In 1530, the great Veronese physician Girolamo Fracastoro published a poem describing a shepherd named *syphilus* who disturbed the altars of the Sun-god (see illustration). As punishment for this desecration, the great pox descended upon him. A dubious immortality was thus conferred upon this humble shepherd when his name replaced the great pox as the accepted title for the disease.

Numerous parallels can be drawn between the illnesses of syphilis and AIDS.

Both are essentially venereal disorders and each had been a previously unknown pestilence—at least to the Europeans and their Western Hemisphere descendants; both, at least initially, were highly lethal sicknesses; and in the early years of encounter, both prompted excessive and irrational communal responses including recommendations for such indefensible measures as branding, imprisonment and exile. And with both disorders, finally, preventive measures provided the only reliable barriers to further infection until curative agents became available.

Stanley M. Aronson, MD

From Triptychs To T-shirts

A Nobel Prize winner in physics, Professor Leon Lederman, commenting on the search for the ultimate particle of matter, says that this hypothetical quark-like particle, "orchestrates the cosmic symphony." He expresses the hope that with its discovery, it will "... reduce the laws of physics to an equation so simple that it can fit on a T-shirt."

There was a time, of course, when the sole purpose of a T-shirt was to provide underclothing for males; and the T-shirt was then judged—if indeed judged at all—by its cleanliness rather than its message. But those days of innocent purpose are gone and the T-shirt has joined the automobile bumper-sticker and the lapel button as the pre-eminent in-your-face bulletin board for proclaiming one's aspirations, affiliations, travels, or even one's views on politics, sex, sports, fishing and religion.

In the beginning of the T-shirt era, the messages were simple, guileless, nonobtrusive, and monochromatic. They declared that you were allegedly attending a particular college, were a member of some beleaguered group (eg, "I Survived the Blizzard of '78") or were professing eternal devotion to some rock singer. As the T-shirt designs became more sophisticated, colors frequently became garish and no visit to Yellowstone Park was considered complete without the purchase of an outrageously tasteless T-shirt for each of the children.

Whimsy often prevailed ("Property of the State Prison.") Some were even faintly amusing ("I'd give my right arm to be ambidextrous."); and a rare one astonishingly perceptive ("Healing is a matter of time, but it is sometimes also a matter of opportunity.") In some domains, though, bad taste prevailed and T-shirts began to explore new limits of socially tolerated expression; the defenders of the First Amendment were then often hard-pressed to defend the T-shirt literati.

The expanding T-shirt industry, inevitably, invaded the domain of the professions. The specialties of medicine, for example, now hawk T-shirts (along with respectable textbooks) at their annual conventions. The ophthalmologic T-shirt might proclaim: "A sight for sore eyes!"; while the proctologic T-shirt boldly announces: "We get to the bottom of things." Surgeons specializing in vertebral dis-

ease invite the readers of their T-shirts to "dance at the Herniated Discotheque." Nephrologists declare grimly: "Urine is Beautiful!" Pulmonary disease specialists, attuned to the latest cultural sea-changes, use their T-shirts to advertise: "Thoracic Park: Where Dinosaurs with Emphysema Go." Geriatricians, more concerned with substantive issues assert: "You know you're old when everything either aches or leaks."

For want of humor, many T-shirt messages have turned to hostile invective. Sometimes, though, a rare T-shirt strolls around the corner with a message on its ventral face of such Franciscan earnestness (eg, "Go To Heaven") that people pause and suspiciously seek some cynical counterpoint on the dorsal T-shirt surface. And when none appears, they walk away in bewilderment.

Each age and culture has been burdened, sometimes blessed, with fervent, typically gratuitous, messages on its unadorned surfaces. The T-shirt, of course, is not the only surface upon which to express one's views. We have carved initials on the trunks of beech trees; and,

Letter to the Editor

Physicians and Suspected Rabies

To the Editor:

On July 6, 1993, a rabid racoon was found in Oxford, Massachusetts, 10 miles north of Burrillville, Rhode Island.

Since September 1992, the following rabies-confirmed animals have been identified in Massachusetts: 284 racoons, 3 cats, 2 foxes, 15 skunks, 4 woodchucks and 1 cow. Massachusetts is averaging a dozen post-exposure prophylaxis treatments a week.

Connecticut is averaging 60 rabies-confirmed animals a month (raccoons, skunks, cats, woodchucks, dogs, foxes, sheep, cows, horses) and close to 400 humans have undergone post-exposure treatment.

The Rhode Island Rabies Control Board recently passed new regulations to help local and state agencies in handling this problem. The designated responsibilities for handling the exposing/exposed animals are as follows: Suspect rabid livestock are the responsibility of the state veterinarian (277-2781). Suspect wildlife that can safely be apprehended are the jurisdiction of the Department of Environmental Management, Division of Enforcement (277-2284). Suspect rabid dogs, cats and ferrets are the responsibility of the local animal control officer. These officers have been trained in the

as a further yearning for immortality, painted statements on railroad overpasses (eg, "Tristan loves Isolde.") But each in its own fashion says: "You didn't ask; nevertheless I insist that you read me; I have something important to tell you!"

These various exhortations have sometimes been lofty, sometimes profane, occasionally even scatologic; some have lingered as hieroglyphic carvings on Egyptian steles, as religious imageries on altar triptychs, or even as spray-painted graffiti on urban facades. Some, too, are spiritually moving; some incomprehensible; others, utterly tasteless; but a few—a very few—say something of such transcendent importance that the defacing of a clean surface is justified. Shelley tells of an abandoned statue pedestal with this sculpted graffiti:

'My name is Ozymandias, king of kings:
Look on my works, ye Mighty, and
despair!'

Nothing beside remains. Round the decay
Of that colossal wreck, boundless and
bare,

The lone and level sands stretch far away.

Stanley M. Aronson, MD

management of suspect rabid animals. The disposition of the attacking (or attacked) animals is determined by the aid of the new rabies regulations and the Rhode Island Rabies Management Manual. Copies are available from the State Veterinarian's office.

These officials *must be notified* by the physician who attends a bite victim. The animal may then be located and euthanized or quarantined. Capture and identification of the biting animal may avoid the costly and painful postexposure treatment.

The Infectious Disease Division of the R.I. Department of Health (277-2577) *must be notified* of any bite incidents. Trained epidemiologists are on the staff to help the attending physician determine the need for post-exposure treatment.

Thus far, the mid-Atlantic states racoon rabies epizootic has not claimed a single human life.* Working together, Rhode Island physicians and state and local authorities can maintain this record.

Susan Littlefield, VMD
Rhode Island Public Health
Veterinarian

*(Since this letter was received an 11-year-old girl died of rabies in upstate New York.—Ed.)

AIDS in the '90s: Increasing Clinical Challenges and Constructive Responses

Kenneth H. Mayer, MD

Barbara A. DeBuono, MD, MPH

In July 1990, the RHODE ISLAND MEDICAL JOURNAL published its first issue specifically focused on the clinical problems posed by the local AIDS epidemic. Since then, the number of Rhode Islanders with AIDS has doubled to almost 700. The increasing numbers partially reflect earlier behavioral and demographic trends, ie, individuals who engaged in unprotected sexual contact or shared injection drug use equipment in the early and mid-1980s, whose immune systems subsequently have been compromised by HIV. However, since January 1993 the increase in the number of cases of persons reported with AIDS also reflects a change in the Centers for Disease Control and Prevention's AIDS case definition.¹ All HIV-infected individuals whose CD4 lymphocyte counts have declined to 200 cells/mm³ or less are now classified as having AIDS, whether or not they have manifested HIV-related symptomatology. In addition, independent of CD4 count, HIV-infected patients with any type of active tuberculosis, recurrent bacterial pneumonias, or invasive cervical carcinoma have been reclassified as meeting the new AIDS definition.

The reason for these changes reflects more than simply a "numbers game." Certain pieces of federal legislation, such as the Ryan White CARES Act, contain formulas for funding in local and state jurisdictions that are determined by the number of persons with AIDS. Another aim of the expanded case definition is to enhance the Public Health Services's ability to track the course of the epidemic in a more comprehensive manner. Specific opportunistic illnesses that occur in HIV-infected persons may require added ex-

penditures and health resources, in part because of resistance to currently available therapy leading to a propensity for relapse. Unfortunately, all too often, individuals who are determined to be HIV-positive without the diagnosis of AIDS neither receive adequate services nor can afford needed care until they meet the AIDS case criteria.

Even if the Centers for Disease Control and Prevention had not changed the definition of AIDS, the interpretation of the numbers of AIDS cases will always be an inexact science at best. The number of people with AIDS is partially a function of the HIV-associated behavioral risks prevalent in any group at any time and the ability of early therapeutic interventions to delay the progression of HIV-associated immunocompromise and associated morbidity. Given these complex and dynamic variables, it is no wonder that predictions of the future of the epidemic have to be fuzzy, reflecting the attempt to define a moving target, with secular trends going in different directions.

One of the encouraging take-home messages of this issue of RHODE ISLAND MEDICINE is that we continue to have more therapeutic options available for people living with HIV. The article by Dr Michael Stein and his colleagues emphasizes that AIDS and HIV patient management issues are no longer the arcane province of the subspecialist. AIDS embodies the paradigm of a chronic, debilitating illness. The generalist can effectively integrate the patient's care with infectious disease and other medical specialists, dedicated nurse clinicians, social workers and other mental health professionals, nutritionists, and a wide array of community-based resources. The articles by Dr Flanigan, Dr Smith, and their colleagues, reflect the recent changes in the demographic trends of the epidemic. We must be aware that AIDS in North America is increasingly a clinical problem of vulnerable women and their offspring. The articles also reflect the grow-

... often, individuals who are determined to be HIV-positive without the diagnosis of AIDS neither receive adequate services nor can afford needed care until they meet the AIDS case criteria.

ing expertise and sensitivity of local clinicians who have dedicated themselves to the complex sociomedical needs of women, children, as well as men living with HIV.

The expansion of the HIV epidemic in Rhode Island into new communities has led to the development of increased expertise on many fronts, not the least of which has been the capacity of Brown University AIDS Program (BRUNAP) clinicians to initiate and participate in trials of promising new therapies for patients living with AIDS and HIV. If one uses the syphilis analogy, the currently available medications may be more efficacious and less toxic than arsenicals but are not yet at the "penicillin" stage. Therefore, the need for ongoing meticulous clinical investigation invariably exists.

Moreover, the goals in the medical management of people living with HIV are quite complex and include the attempts to find optimal drug therapies to suppress HIV replication, attempts to ameliorate or reconstitute the immune dysfunction, and the need to treat, and preferably prevent, a myriad of opportunistic infections when individuals become severely immunocompromised. Besides opportunistic infections, HIV itself can cause debilitating symptoms including neurocognitive deficits and a wasting syndrome. Many of the drug trials in BRUNAP have been directed at evaluating promising treatments that may improve these parameters that are so importantly associated with improved quality of life for people living with AIDS and HIV. This state needs a well integrated and comprehensive clinical trials program in AIDS. In her paper, Dr Skowron, the BRUNAP clinical trials

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ABBREVIATIONS USED:
AIDS: Acquired immune deficiency syndrome
BRUNAP: Brown University AIDS Program
HIV: Human immunodeficiency virus

For Further Information

For more information regarding HIV counseling and testing facilities available in Rhode Island, please contact the Department of Health's AIDS/STD Division at 401-277-2320; for more information about AIDS-related clinical trials, please contact the Brown University AIDS Program Clinical Trials information line at 401-456-AIDS or the Brown University AIDS Program office at 401-863-1725.

coordinator, delineates the current efforts that are under way, including trials that are ongoing totally within the Brown system, and those that involve collaborations with several national treatment networks, such as the American Foundation for AIDS Research's Community Based Clinical Trials Network.

The slope of the HIV epidemic curve in Rhode Island and elsewhere is and will be, partially a function of how well our clinical trial efforts succeed, but is also related to the rate of the development of new infections, ie, the risks individuals are taking. To that end, local data leads to cause for concern. An article in the July 1990 issue of the RHODE ISLAND MEDICAL JOURNAL described the New England Behavioral Health Study, an NIH-funded prospective study of the local heterosexual spread of HIV. The analyses thus far indicate that even though more than 2000 individuals were concerned enough about HIV to come in voluntarily to undergo HIV screening without compensation, many individuals were still engaging in high-risk behavior. Among 500 individuals who were invited to return every 6 months to monitor their HIV status and ongoing risk taking activities, 8 new HIV infections occurred. Most of these individuals had HIV infected or high-risk partners but did not routinely engage in safer sex. Several shared intravenous injection equipment. In addition, bi-directional heterosexual HIV transmission was documented. Thus, new infections are occurring even under the best of circumstances, when an individual perceiving him- or herself to be at risk for HIV, comes in for testing and counseling, and follow-up.

We found that some of the major potentiators of ongoing risk-taking behavior included characteristics of the relationship, and coincidental nonparenteral drug use, ie, ongoing problems with alcohol, inhaled cocaine, and other mind-altering substances. An explanation for

this is that the use of intoxicants can impair the negotiating skills that are necessary to continue to maintain vigilance regarding safer sexual practices. Dr Sally Zierler of our team noted that early life events may have marked implications on subsequent risk-taking behaviors, and, in fact, more than 40% of the women and almost 20% of the male participants in the study reported a history of sexual abuse and those individuals were particularly likely to become HIV-infected.²

Improvements in the ability to care for a diverse array of individuals with HIV infection is occurring, but until we have curative therapies and efficacious preventive vaccines, physicians in Rhode Island will continue to have to develop their expertise in the diagnosis, care, and comprehensive management of the com-

plex clinical challenges posed by the AIDS epidemic.

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The Face of AIDS in Rhode Island: Public Health Goals for the 1990s

Mary Lou DeCiantis, PhD

Barbara A. DeBuono, MD, MPH

The primary mission of the RI Department of Health (RIDH) is to protect and promote the health of the population and to prevent disease through lifestyle change, education and health service delivery. The department uses educational, regulatory, financial and programmatic initiatives to pursue this mission.

Rhode Island has a well integrated, organized, service delivery system for the provision of HIV/STD-related counseling and care. All points of contact are centrally located, administered and coordinated. These factors, in combination with density of population and small size make Rhode Island an ideal location to develop a model surveillance, prevention, and treatment program to meet the challenges posed by this epidemic. Case and HIV infection surveillance data are used to plan, implement and evaluate the state's HIV prevention activities.

The department's 1993 goals include:

- Achievement of 100% reporting level for AIDS cases by maintaining proactive follow-up and surveillance efforts, including educating providers on the new expanded AIDS case definition and reporting responsibilities.
- Improve completeness of the HIV Positive Case Registry by working with health care providers to include all pertinent data required on HIV-Positive Case Reports.
- Increase the number of persons counseled and tested at RIDH sponsored or subcontracted sites, such as STD clinics, TB clinics, and substance abuse treatment facilities. In 1992, 29,488 were tested for HIV of whom 416 (1%) were positive.
- Continue ongoing programs to educate health care professionals, target high-risk populations, and the general public regarding AIDS/HIV infection, transmission and prevention.

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To accomplish these goals, the RIDH is actively pursuing grants that would:

- Increase funding to minority community-based organizations to deliver programs to serve minority groups. This is a priority because more than 52% of the HIV+ case reports submitted to the RIDH are people of color.
- Develop and implement surveillance and prevention programs targeted at women, high-risk youth and children. The rate of increase in HIV infection and AIDS in women of child-bearing age is of concern on both state and national levels.

Surveillance and Epidemiology Since 1983

Through 1992, the first decade of AIDS reporting in Rhode Island, 650 cases were reported to the RIDH. However, on December 18, 1992, the Centers for Disease Control and Prevention (CDC) published an expanded surveillance case definition for AIDS among adolescents and adults in the United States. The new case definition is now used by all states and territories and is expected to increase reported AIDS cases by 20% to 30% nationwide.

The expanded AIDS surveillance case definition retains the reporting criteria listed in the 1987 AIDS case definition, but now includes all HIV-infected persons with the following conditions:

- A CD4⁺ T-lymphocyte count <200 cells/uL (or a CD4⁺ percent of lymphocytes <14);
- Pulmonary tuberculosis;
- Recurrent pneumonia (within a 12-month period); or
- Invasive cervical cancer.

The expanded surveillance case definition is expected to have a substantial impact on the number of reported AIDS cases. The immediate increase in case reporting will be largely attributed to the addition of severe immunosuppression (ie, CD4⁺ T-lymphocyte count less than 200/uL or CD4⁺ percent less than 14) to the surveillance definition; a smaller

All HIV-related and other health care information will be protected in accordance with all relevant federal and state laws relating to confidentiality of health care administration.

impact is expected from the addition of pulmonary TB, recurrent pneumonia, and invasive cervical cancer, since many persons with these diseases will also have less than 200 CD4⁺ T-lymphocytes/uL.

If the AIDS surveillance criteria had remained unchanged, about 100 reported AIDS cases would have been expected in Rhode Island in 1993. The RIDH estimates that the expanded definition could increase AIDS cases reported in 1993 by as much as 200%, resulting in, perhaps, a total of 300 cases reported in 1993. Sixty-two newly diagnosed cases of AIDS have been reported to the RIDH from January 1 through February 28, 1993, compared to 11 reported for the same time period in 1992. Of these 62 cases, 31% (19) are female and 69% (43) are male. Of the females, 37% (7) are black, 47% (9) white, and 16% (3) Hispanic; of males, 39% (17) are black, 33% (14) white, 26% (12) Hispanic, and 2% (1) is a Native African Indian. Half (31) are IV drug users, 26% (15) homosexual males, 16% (10) heterosexual, 17% (4) hemophiliacs, and 3% (2) are IV drug users and homosexual.

Since AIDS case reporting was implemented in Rhode Island in 1983, through 1992, the primary mode of transmission has been homosexual behavior (47%), followed by IV drug use (30%). Females represented 13% to 16% of cases reported each year. The preliminary data for 1993 indicate that the face of the

ABBREVIATIONS USED

AIDS: Acquired immune deficiency syndrome

CDC: Centers for Disease Control

HBV: Hepatitis B virus

HIV: Human immunodeficiency virus

HRSA: Health Resources Services Administration

IVDU: Intravenous drug user

OSHA: Occupational Safety and Health Administration

RFP: Request for Proposal

STD: Sexually transmitted disease

TB: Tuberculosis

epidemic in Rhode Island is changing significantly. This trend toward an increase in reported cases in women and IV drug users and their sex partners, will represent important public health challenges.

The new AIDS surveillance case definition could help extend lives, especially among women. AIDS in many women has often been overlooked because AIDS was first recognized among gay men, and the diseases they commonly got defined AIDS. Health problems more common to women who are HIV positive, such as cervical cancer, pelvic inflammatory disease and vaginal yeast infections were ignored.

Women, unknowingly, may carry the virus for years because HIV testing is not always a part of a routine screening. Gynecologists should be aware of recurrent pelvic inflammatory disease and vaginal yeast infections as possible indications for the presence of HIV. These conditions should send up warning flags that women should be tested for HIV.

AIDS Program Goals

The Office of AIDS/STD issued a Request for Proposals (RFP) in October 1992 to develop and implement projects related to three areas of prevention education with emphasis on communities of color: public education using local and statewide media; health education/risk reduction using creative techniques to empower and mobilize communities of color; and comprehensive outreach services to include counseling and testing, medical, and psycho-social services. Of the 27 proposals submitted, 11 were awarded more than \$300,000 in federal funding.

Subject to the availability of state funding, the Office of AIDS/STD anticipates issuing a second RFP within the next 1 to 2 months. This RFP will solicit proposals to provide case management to HIV-infected persons, HIV counseling and testing, and public education initiatives. The RIDH expects to award approximately \$500,000 to community-based organizations and health care providers to provide AIDS counseling and testing services, public education and case management services. These dollars, awarded through competitive bidding, are targeted to address high-risk groups in the population with preventive services.

The RIDH Division of Disease Prevention and Control is well prepared to manage the challenge to its surveillance

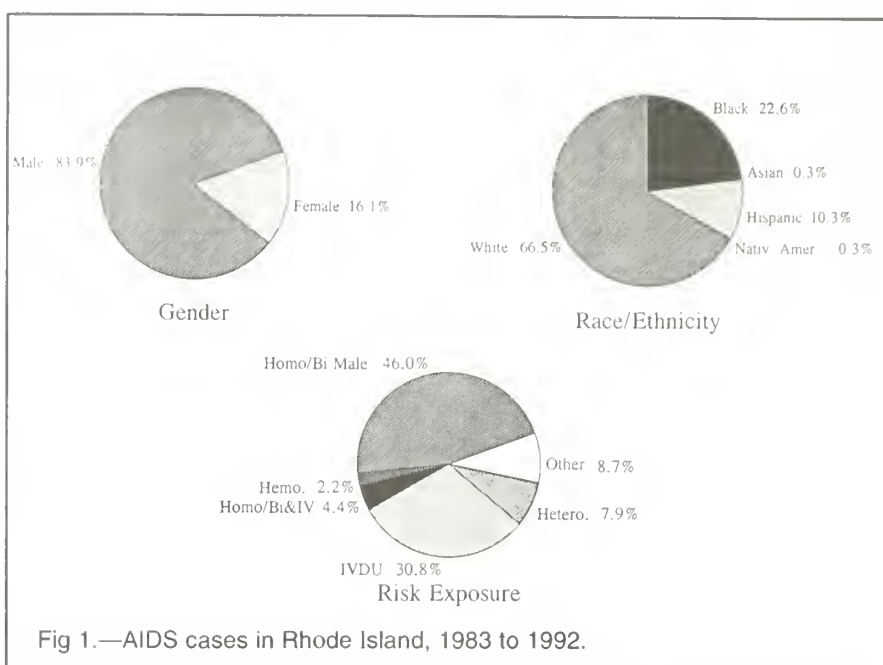


Fig 1.—AIDS cases in Rhode Island, 1983 to 1992.

programs posed by the expanded AIDS case definition. For example, the division includes the Offices of AIDS/STD and the tuberculosis and cancer programs, which are administered and physically located in joint offices. TB and cancer reports can be accessed and surveyed for HIV infectivity status. The physician can then be contacted by the Health Department staff to discuss the clients' status anonymously.

Rhode Island's HIV Infected Health Care Workers Policy

New state guidelines regarding HIV- and HBV-infected health care workers were issued by the RIDH, in response to the CDC requirements. The guidelines, which emphasize the extremely low risk

of transmission to patients by HIV- or HBV-infected health care workers, include the following policy statements:

- Mandatory HIV or HBV testing will **not** be required for health care workers;
- Mandatory continuing education requirements on universal precautions, infection control, and OSHA blood-borne pathogens for physicians and dentists;
- The formation of a state panel to review, advise, and monitor, on a voluntary and confidential basis, infected health care workers practicing in Rhode Island;
- The RIDH will not list specific hazardous procedures, but will judge each case on an individual basis; and
- All HIV-related and other health care

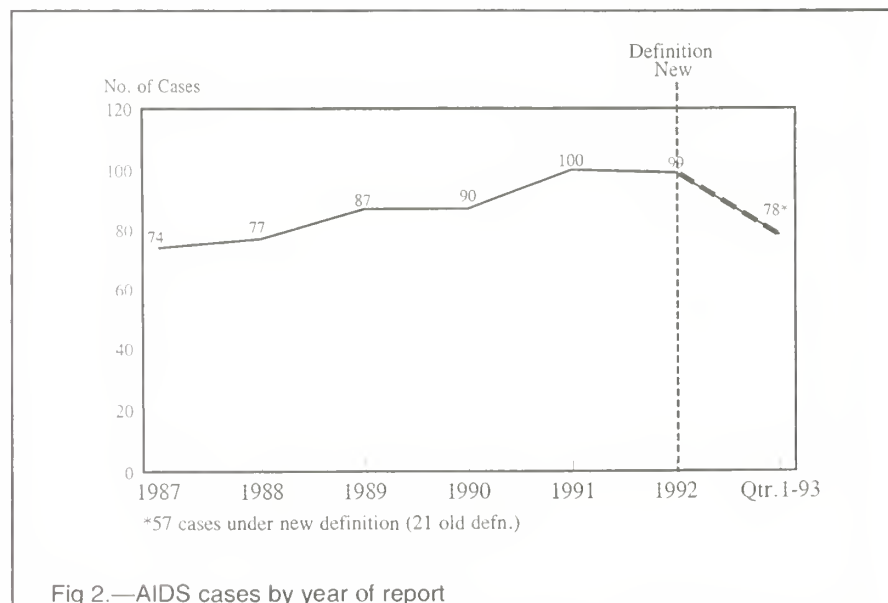


Fig 2.—AIDS cases by year of report

information will be protected in accordance with all relevant federal and state laws relating to confidentiality of health care information.

Mandatory continuing education requirements for universal precautions, infection control, and OSHA blood-borne pathogens have been instituted: for physicians, 2 hours every 3 years; for dentists, 3 hours every 3 years.

New Surveillance Initiatives

AIDS surveillance is the primary means in Rhode Island for tracking the HIV epidemic. In addition, Title II funds awarded to state health departments by the Health Resources Services Administration (HRSA), under the Ryan White CARE Act, are distributed through a formula grant based on reported AIDS cases. Accurate, timely, and complete AIDS case reporting is important to assure both the proper assessment of the epidemic and the allocation of funds needed to provide critical services to HIV-infected persons in our state.

To revise state surveillance initiatives to respond to the new CDC reporting requirements, the RIDH filed "Emergency Rules and Regulations Pertaining to the Reporting of Communicable and Environmentally Related Diseases." This regulation became effective immediately upon filing.

The emergency regulations stipulate the following regarding AIDS reporting.

- Physicians or their designees shall report all findings on tests for T-helper (CD4+) lymphocyte counts on any person with HIV infection to the Office of AIDS/STD.
- Persons reporting T-helper counts shall not be required to report the name of the patient or other information that would identify the person tested if the count is 200/uL or above.
- If the T-Helper count is less than 200/mL, the physician shall report the test result as a case of AIDS to the Office of AIDS/STD.
- Upon submission of this case report, no further T-cell reports need to be submitted to the Office on this patient.
- Whenever a laboratory performs CD4+ lymphocyte tests or has the samples tested out of state, reports of counts less than 200/uL shall be reported directly to the Office of AIDS/STD. The form shall contain the name of the patient/client, the name of the physician, and the date of the test, and shall be mailed directly to the Office of AIDS/STD.

Conclusion

Rhode Island's AIDS Program is comprehensive and multi-faceted. Monitoring this changing epidemic, preventing its spread, and providing referral and care coordination to persons living with HIV remain the Department of Health's paramount goals. Forging relationships with AIDS service providers and communities affected by this disease will

position the health community to better adapt to the changing face of AIDS during its second decade.

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Federal/State Expenditures for HIV/AIDS Services

Mary Lou DeCiantis, PhD

Barbara A. DeBuono, MD, MPH

With incidence levels expected to double in the next 2 years, substantially more money must be appropriated at both the federal and state levels.

Since 1986, the AIDS Policy Center of the Intergovernmental Health Policy Project at George Washington University has conducted survey research to ascertain the amount of state funds devoted to HIV/AIDS programs and services. Data are collected on both federal and state, non-Medicaid expenditures across six program areas: Education, Information and Prevention; Testing and Counseling; Research; Surveillance; Health Care and Support Services; and Administrative Activities. The figures reported generally capture only the funds supporting programs operated by the Health Departments within each state. Therefore, state funds reported across the program categories most likely underestimate expenditures dedicated to the epidemic.

Spending Patterns

Table 1 details state expenditures across the six program categories, as well as total funds expended.

Table 2 details Health Care and Support Services Spending Per Person Living with AIDS. Spending per person living with AIDS was derived by divid-

Table 1.—Distribution of Rhode Island State Funding for HIV/AIDS by Program Category Fiscal Year 1992

Education Information	\$23,285
Testing/Counseling	\$406,925
Research	\$0
Surveillance	\$32,193
Health Care/Support Services	\$484,00
Administration	\$75,794
Total: State Funds	\$1,022,197
Cumulative Cases 1992	535

'Source: AIDS Policy Center, Intergovernmental Health Project, The George Washington University, April 1993

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Table 2.—Rhode Island Health Care Support Services Spending Per Person, Living With AIDS

	FY 1991	FY 1992
Health Care/Support Services	\$372,533	\$484,000
Cumulative Cases	411	535
Estimated # Living Persons with AIDS	150	180
Spending per Living Person with AIDS	\$2,476.52	\$2,684.49
Percent Change	Not applicable	8.40%

'Source: AIDS Policy Center, Intergovernmental Health Project, The George Washington University, April 1993

ing patient care/support services funds by an estimate of the number of persons living with AIDS. The data reveal a slight increase in per person spending, from \$2,476 in FY1991 to \$2,682 FY1992, which can be attributed to the increases availability of federal funds under the Ryan White CARE Act, which supports treatment services.

Per Capita Spending

Expenditures for Education, Testing and Counseling, and Surveillance were combined as a measure of per capita spending for prevention. In FY1992, average per capita spending for prevention measures was \$0.65, a significant increase over the FY1991 level of \$0.51. However, per capita spending for prevention in Rhode Island is lower than the national average at \$0.46.

A rank order of both total and per capita HIV/AIDS funds, however, presents a different picture of per capita spending. While Rhode Island ranks 29th in the nation in terms of total funds, it is 15th in per capita spending. Trends in per capita funds from 1989 through 1992 are depicted in Table 3. In New England,

most states maintained stable per capita funds over the 4 years. Of note is Massachusetts with a significant increase from FY1989 to FY1990, while Rhode Island experienced a significant decrease.

State funding allocated to the Office of AIDS/STD within the RIDH, has decreased from \$2.9 million in 1989 to \$1.1 million in 1993, while the number of AIDS cases has increased more than 40% during the same time period.

State statistics reveal that 1.3 Rhode Islanders become newly infected with HIV each day, and project that by the end of 1993, cumulative AIDS cases in Rhode Island will exceed 1000. State funded HIV/AIDS programs are, in most cases, unable to meet current demands, especially for health care and support services. With incidence levels expected to double in the next 2 years, substantially more money must be appropriated at both the federal and state levels.

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Table 3.—Trends in Per Capita State HIV/AIDS Funds New England States, Fiscal Years 1989 - 1992

States	FY89	FY90	FY91	FY92
Connecticut	\$2.12	\$1.87	\$2.48	\$2.68
Maine	\$0.33	\$0.38	\$0.42	\$0.57
Massachusetts	\$2.51	\$3.08	\$3.03	\$3.12
New Hampshire	\$0.29	\$0.25	\$0.26	\$0.23
Rhode Island	\$2.88	\$1.58	\$0.91	\$1.02
Vermont	\$0.00	\$0.04	\$0.04	\$0.42

'Source: AIDS Policy Center, Intergovernmental Health Project, The George Washington University, April 1993



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The Management of HIV-infected Patients

By Primary Care Providers

Michael D. Stein, MD

Alvan E. Fisher, MD

Tom J. Wachtel, MD

The number of people infected with human immunodeficiency virus in America continues to rise. During the past 2 years the number of new AIDS cases equalled the number reported in the first 10 years of the epidemic. At the same time, HIV-infected persons are increasingly found in smaller urban, suburban and rural areas rather than the major metropolitan areas that characterized the early years of the epidemic. While the majority of care for infected persons is still centered in major academic centers, community physicians are increasingly likely to have at least one person infected with HIV among their patients.

The characteristics of HIV care fit the demands of primary care: comprehensiveness, continuity, attention to psychosocial concerns and coordination with consultants. Yet half of American primary care physicians would, if given the choice, prefer not to care for persons with HIV infection.¹ A primary care physician's decision to become reasonably involved in the care of large numbers of HIV-infected patients depends on several factors, but the two most common barriers to the caring of HIV-infected persons cited by physicians are the perception that they lack adequate information about AIDS, and that AIDS care takes too much time.¹

Unlike 5 years ago, the care of HIV-infected persons now occurs primarily in the outpatient setting. Patients generally receive HIV testing earlier after infection and therefore have longer symptom-free periods than even 5 years ago. While an understanding of the natural history of HIV infection has increased and new treatment options have been developed, the information needed to develop a

medical management plan for the asymptomatic patient is easily assembled by the primary care practitioner. The basic components of a treatment plan will make up the second part of this article. The first, and harder step, is talking to patients about AIDS and determining who may be at risk for HIV. Early diagnosis will not only optimize therapeutic options for patients and postpone serious HIV-related complications but also may curb high-risk behavior.

Who Is at Risk?

During the past decade, universal compulsory screening for HIV has not occurred for ethical, legal, and practical reasons. Instead, screening efforts have been recommended for those at "increased risk" for HIV infection, with patients and physicians making their own judgments as to this risk.

We believe that there are now three sets of clues for evaluating HIV risk.² The first focuses on patient behaviors gathered during the medical interview, the second considers specific aspects of a patient's clinical history, and the third examines laboratory data that may be available from previous medical encounters or can be simply collected at an office visit (Table 1).

History-taking serves the practitioner not only as the first line of risk assessment but also as a means for counseling about self-care and health habits. Nevertheless, surveys have demonstrated that only a minority of physicians take sexual histories from new patients, and that inquiries are most often related to difficulties with sexual function. Clearly, a thorough sexual history that explores sexual behavior is necessary to assess HIV risk. Persons whose activities place them at risk for HIV infection include men who have had sex with a man, intravenous drug users who have shared needles, persons who received blood products (particularly before 1985), health care workers who perform invasive procedures, and the sexual partners of any of the above. All physicians have difficulty gathering this sensitive information and

During the past 2 years, the number of new AIDS cases equalled the number reported in the first 10 years of the epidemic.

repeated discussions with individual patients may be necessary over time. Patients may not acknowledge activities that put them at risk for HIV infection; they rarely know the HIV status of all previous sexual partners. However, education can take place during history-taking. Patients may not know that unprotected anal intercourse is an efficient route of HIV transmission or that latex condoms are recommended over other varieties.

Specifics of the patient's past medical history may provide additional clues for HIV-risk assessment. Persons who have had unexplained, persistent constitutional symptoms, recurrent bacterial pneumonias, previous episodes of sexually transmitted diseases, tuberculosis, *Herpes zoster*, and women with recurrent and increasingly frequent episodes of vulvovaginal candidiasis should be urged to have HIV testing. These conditions may be clinical indicators of HIV infection, although none of these conditions is specific for HIV.

Finally, certain laboratory tests serve as clues to HIV infection. Hepatitis B screening is performed commonly during pregnancy, and results may be avail-

ABBREVIATIONS USED

AIDS: Acquired immune deficiency syndrome

AZT: Zidovudine

BUN: Blood urea nitrogen

CBC: Complete blood count

CME: Continuing Medical Education

CXR: Chest X-ray

ddC: Zalcitabine

ddI: Didanosine

ELISA: Enzyme Linked Immunosorbent Assay

FDA: Food and Drug Administration

HIV: Human immunodeficiency virus

MAI: *Mycobacterium avium-intracellulare*

PCP: *Pneumocystis carinii pneumonia*

PPD: Purified protein derivative

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able for reproductive age women. This virus is sexually transmitted, and is highly prevalent among injection drug users; a positive serology should suggest the need for further history-taking. Persistent thrombocytopenia now includes HIV infection in its differential diagnosis, and persons with low platelet counts should be counseled about HIV testing. Finally, women with high-grade squamous intraepithelial lesions in cervicovaginal specimens should be considered for HIV counseling and testing.

Physical Examination

Although HIV and its complications may involve nearly every organ, a general physical examination is not a sensitive screening tool for HIV infection. A directed physical examination should focus on: 1) the skin; 2) the mouth; 3) the anogenital region; and 4) the nervous system.

The skin may be involved early in the course of HIV infections. Common skin disorders include viral infections (*Herpes simplex*, *Herpes zoster*, molluscum contagiosum), fungal infections, bacterial infections (including syphilis), and inflammatory disorders such as severe or new-onset seborrhea and psoriasis. The oral cavity is often the site of manifestations of HIV disease. Findings include candidiasis, herpetic lesions, leukoplakia (plaques on side of tongue) and aggressive periodontitis. The genitalia and rectum should be examined for the presence of sexually transmitted diseases. The neurologic system is involved in many patients with HIV disease because HIV itself and complicating opportunistic infections (such as toxoplasmosis) have an affinity for nervous tissue. A careful baseline neurologic examination is important and should include a formal mental status examination.

HIV Counseling and Testing

The ordering of an HIV test should always be preceded by counseling because patients who receive a positive test result often cannot comprehend information at the time of the result (Table 2). Patients commonly have misconceptions about the test. They should be told that a positive test does not imply AIDS, but rather infection with the virus that causes AIDS and while they may remain asymptomatic for many years, they may transmit the virus sexually, by donating blood, or by shar-

Table 1.—Candidates for Human Immunodeficiency Virus Testing

Social and Sexual History

- Men who have had sex with a man.
- Intravenous drug users who have shared needles.
- Recipients of blood transfusions or products (1978-1985).
- Sex partners of any of the above.
- Some sexually active heterosexual women.
- Health care workers who perform invasive procedures.

Clinical History

- Unexplained persistent constitutional symptoms
- Recurrent vulvovaginal candidiasis
- Previous episode of syphilis, chancroid, gonorrhea, or herpes simplex
- Diagnosis of tuberculosis
- Recurrent bacterial pneumonia
- Herpes zoster*

Laboratory Tests

- Serologic evidence of hepatitis B markers
- Autoimmune thrombocytopenic purpura
- Abnormal Papanicolaou (squamous intraepithelial smear lesions)

ing needles for illicit drug use. It is important to gauge what the patient knows about HIV, what they expect their test result to be, and how they might cope with a positive test. Patients should be encouraged to identify one person who knows that they are being tested and what they plan to do following receipt of the test result.

Test recipients should be told that while very accurate (sensitivity and specificity of the combined ELISA and Western Blot test, which most laboratories perform on a single submitted sample, exceed 99%), the predictive value of a positive HIV antibody test will be low in low-risk persons.³ Causes for false positive test results include chronic liver disease, autoimmune disease, and infections with other retroviruses. The most common cause of false negative results is testing soon after infection during the "window" of seroconversion (ie, the virus is present but not enough time has elapsed for antibody production).

Post-test counseling of all HIV test results should be done in person, never by telephone. Counseling of HIV-positive individuals should focus on the emotional consequences of learning test results and should include the development of a social support plan. Physicians should

make available information on local counseling services. A medical treatment plan may be outlined at the first post-test visit or may be delayed until a later visit. Finally, a discussion of sexual partner notification should take place. The state Health Department may provide assistance with this task if patients are unwilling to notify past and current partners themselves.

Post-test discussion with an HIV-negative patient should include possible behavior change, condom use, drug treatment if needed, and the possibility of future HIV testing if high-risk behavior has occurred recently.

Medical Assessment and Treatment

The CD4 (T4, T-helper) lymphocyte is a direct target of HIV, and its count is the most widely used indicator of a patient's level of immunodeficiency. The CD4 cell count is currently used to guide decisions regarding both antiretroviral therapy and prophylaxis against opportunistic infections.⁴

It is useful to stratify patients into three groups according to their CD4 cell count. Because there is variability in CD4 results (usually ordered as a T-cell profile) depending on laboratory experience, intercurrent infection, and even time of day drawn, treatment decisions should be based on several values. Having greater than 500 CD4 cells/mm³ indicates a robust immune system; patients with such counts almost never have HIV-related symptoms. Below 500 and above 200 cells/mm³, patients become more susceptible to bacterial and minor fungal infections. Below 200 cells/mm³ patients are most susceptible to a panoply of opportunistic infections and prophylactic regimens should be implemented.⁵

Antiretroviral Therapy

Three viral reverse transcriptase inhibitors are currently FDA-approved as antiretroviral agents: zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC). Zidovudine is the most widely used first line agent, and may be initiated in patients with CD4 counts of 500 cells/mm³ or less even if patients are asymptomatic.⁷ The usual daily dose is 500mg to 600mg, given between three and five times daily. The most common side effects—nausea, headache, and insomnia—can be managed symptomatically and

most often disappear within weeks of starting treatment. Many of patients receiving AZT develop macrocytosis and its presence signals compliance. Severe anemia can occur with AZT, requiring drug discontinuation, dosage lowering, or a trial of erythropoietin; leukopenia occurs in persons with advanced disease.

ddI is approved for those patients with symptomatic disease. It is usually administered at a dose of two 100 mg tablets twice daily and should not be taken with food. The major adverse reactions associated with ddI are pancreatitis and peripheral sensory neuropathy. Because hematologic side effects are less common, ddI can be given to persons who have this adverse effect with AZT.

ddC has been approved for use in combination with AZT for patients with CD4 counts below 300 cells/mm³. The recommended dose is 0.75 mg TID. ddC has a side effect profile similar to ddI, although the incidence of pancreatitis is lower with ddC.

Viral resistance develops after prolonged treatment with any of these three agents. Clinical associations with viral resistance are difficult to establish, but substitution or addition of antiretroviral agents should be considered after continuous treatment of 1 to 2 years, or if CD4 cell counts show a dramatic decline over a short time while on therapy.

Pneumocystis carinii pneumonia prophylaxis

Pneumocystis carinii pneumonia (PCP) remains the most common opportunistic infection among persons with AIDS.⁸ To prevent this complication, when the CD4 count falls below 200 cells/mm³, oral sulfa-trimethoprim (Bactrim) is recommended at a dose of one double-strength tablet daily or every other day. This regimen has been shown to be more effective than the alternative, aerosolized pentamidine (300mg/month), in preventing PCP. Oral dapsone (50mg/d) has been less well studied, but may be as effective as aerosolized pentamidine, and is also commonly prescribed as the second line agent for PCP prophylaxis.

Additional Prophylactic Strategies

At CD4 cell counts below 100 cells/mm³, patients are most vulnerable to the full variety of opportunistic infections. At this time, many clinicians offer additional forms of prophylaxis. Rifabutin (300mg/d) has recently been approved to prevent systemic *Mycobac-*

Table 2.—Suggested Counseling Steps Before and After HIV Testing

Pre-Test Counseling

1. Explain what an antibody test result means
2. Explain the advantages of knowing one's antibody status in terms of medical management
3. Explain risk behaviors and how to reduce risk, including condom use.
4. Learn what your patient expects the result to be
5. Ask how your patient will cope with positive test
6. Discuss the importance of partner notification
7. Patient should be encouraged to identify one person who knows they are being tested and with whom they can discuss the test result

Post-Test Counseling

1. Always in person
2. After giving the test result, let your patient express feelings and concerns
3. Develop a social support plan including return visit
4. Give information on medical treatment and counseling services

terium avium-intracellulare (MAI) infection, a progressive, systemic infection characterized by fevers, diarrhea and weight loss. Rifabutin may decrease the incidence of this infection up to 50%; common side effects include nausea and rashes but is generally well tolerated. Similarly, Fluconazole (100-200mg/d) has been used to prevent two infections: cryptococcosis and candidiasis. Prolonged administration of either of these agents may lead to resistance of organisms and breakthrough infections, but most clinicians and patients prefer to take this risk.

Vaccinations

Patients with HIV should be kept up to date with vaccinations.⁹ All patients should receive pneumococcal vaccine once, as early during illness as possible to increase the likelihood of developing protective antibodies. Influenza vaccine should be given yearly. Hepatitis B vaccination should be reserved for patients whose behavior places them at risk for infection and who show no laboratory signs of previous immunity. Tetanus vaccination should also be kept up to date.

Ongoing Primary Care

The complexity of HIV disease re-

quires regular assessment of both the physical and psychosocial needs of patients. Primary care issues such as screening for tuberculosis and gynecologic cancers must be addressed with all patients, and the Centers for Disease Control have published recommendations in many areas. But there are few recommendations published regarding more general clinical practices. A survey of practice patterns among practitioners caring for patients with HIV disease did yield considerable agreement in practice norms (Table 3).¹⁰ Managing the HIV-positive person requires attention to a comprehensive care plan and depends on the clinical stage of illness with return visits and laboratory testing becoming more frequent as the CD4 count declines. The severity of an individual's illness and the number and types of medications used will also dictate the care plan. These guidelines can easily be managed by the primary care provider.

Private Office Practice

Although the primary care of most patients with HIV infection has been centered at academic hospitals, in many cities patients may also choose to seek care from physicians with private office-based practices. HIV infection and AIDS pose special problems for both patient and physicians in such a setting. Surveys have revealed that many primary care patients would prefer not to go to a physician who care for patients with AIDS. The persistent perception that HIV can be transmitted by casual contact even in physician waiting rooms, complicates office practice. It is critical for the physician to be open about the nature of his or her practice to diffuse irrational fears and concerns and to educate about HIV infection. Patients without HIV infection will readily accept care in an office setting where AIDS care is provided if the physician maintains interest and concern about their medical problems and does not attempt to hide his professional involvement with HIV-infected patients.

The patient with HIV infection (like others without HIV infection) should welcome care given in a comfortable, confidential setting. Many patients with HIV infection feel stigmatized by prejudice and ignorance and will seek out the most appropriate settings and providers. It is crucial that all office staff are fully educated about HIV infection, especially transmission and psychosocial consequences to foster understanding at all encounters. Office staff also need to be attuned to patient concerns about confi-

Table 3.—Management of Persons with HIV Disease

	CD4=>500 cells/mm ³	CD4=200-500/mm ³	CD4=<200/mm ³
Routine Physical Examination	every 3 to 6 months	every 3 months	monthly
Pelvic Examination/Pap	every 6 months	every 6 months	every 6 months
Cognitive Testing	every 6 months	every 3 months	monthly
CBC	every 3 to 6 months	every 1-2 months	monthly
BUN and/or creatinine	yearly	every 3-6 months	every 3-6 months
Transaminase, alkaline phosphatase	yearly	every 3-6 months	every 3-6 months
Syphilis serology	once	as often as needed	
CD4 Count	every 3 months		
PPD	yearly	yearly	yearly
CXR	Baseline	for pulmonary symptoms or as otherwise needed	
Pneumococcal vaccine	once		
Influenza Vaccine	yearly	yearly	yearly
Antiretroviral Therapy	no	yes	yes
PCP Prophylaxis	no	no	yes

dentiality.

The physician needs to establish a network of like-minded health care providers for the wide variety of services commonly needed by persons living with HIV, including psychological counseling, nutrition, evaluation, laboratory and imaging services, as well as medical or surgical referrals. Almost all patients with HIV infection will benefit from psychosocial evaluation and counseling, whether private or in a group setting. Family members also may need to be involved or may seek out such counseling. Frank nutritional deficits are common at most stages of HIV infection and require evaluation and intervention by a nutritionist experienced with the effects of HIV infection may be helpful.

Referrals to other medical specialists in such fields as gastroenterology, neurology, oncology, dermatology, surgery and ophthalmology are very common and the same issues of prejudice and stigmatization need to be addressed in the offices of these consultants. Finally, advanced diagnostic (laboratory or imaging) and therapeutic (home infusion) services are regularly required. The convenience and accessibility of these services may greatly enhance patients' acceptance of difficult HIV-related complications. Physicians are integrating some or all of these services into their private offices to enhance patient compliance and avoid fragmentation of care.

The greatest challenge for the physician in private office practice is maintaining an adequate level of knowledge in a field changing as rapidly as HIV disease. Hardly a season goes by without a media report of the latest drug-of-the-month (or week or day) followed by the clamor for further information from patients. Changes in HIV treatment do oc-

cur regularly and need to be integrated into clinical practice. Most practitioners will have trouble digesting the mass of published material on AIDS, but several newsletters covering HIV and AIDS exclusively are readily available. *AIDS Treatment News*, which is published in San Francisco, and *AIDS Clinical Care* from Boston are two publications that report major developments in HIV care that will be useful to both patients and practitioners. Subscribing to these publications as well as attending local or regional medical updates should be adequate for primary care physicians to maintain a state-of-the-art approach to the basic medical care of persons living with HIV. Ongoing AIDS clinical updates are offered several times a year in a variety of formats (lectures, conferences, practica, etc.) with CME credits by both the Brown University AIDS Program (863-1725) and the RI Department of Health (277-2320).

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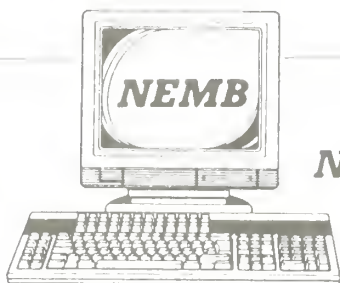
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HIV Infection in Rhode Island Women

Timothy P. Flanigan, MD, Susan Cu-Uvin, MD,
Theresa Fiore, Kevin Vigilante, MD, Janice
Kizirian, MD, Charles C.J. Carpenter, MD

Although most HIV-infected persons in North America are still men, women of reproductive age are the fastest growing segment of the population with HIV infection. In 1985, women accounted for 7% of all AIDS cases; by 1991 they accounted for 13%.¹ In Rhode Island, a considerably larger proportion of individuals with AIDS in 1991 were women compared to national statistics.² AIDS is the fifth leading cause of premature death in US women; in several major urban areas of the Northeast, it is the leading cause of death for women aged 25 to 44. Although we are entering the second decade of the AIDS epidemic, we only now are beginning to have a better understanding of the natural history and complications of HIV infection in women. Initial, prospective cohort studies were carried out almost exclusively on men, and only recently have comparable efforts been directed toward women. There are now vigorous efforts to recruit HIV-infected women for appropriate therapeutic trials and learn more about gender-specific clinical aspects of AIDS.

Changing HIV Patterns in Women

The pattern of HIV transmission has changed dramatically in women since the beginning of the AIDS epidemic. Among US women with AIDS, injection drug use was the primary route of infection for most during the first 6 to 8 years of the epidemic. During the past few years, however, heterosexual transmission has become the dominant route by which women have become infected by HIV in many regions of the United States. Before 1989 in Rhode Island, only 22% of recognized cases of HIV infection in

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women occurred through heterosexual transmission. In 1989, 30% of women acquired HIV through heterosexual transmission. By 1990, this increased to more than 40% and in 1991, just under 50% of women who presented with HIV infection had acquired the disease through heterosexual transmission (Figure 1).⁴

Many women infected with HIV through heterosexual transmission do not perceive themselves to be at "high risk" for HIV. In a multicenter study of HIV-positive blood donors, over a third of women had no identifiable risk beyond limited heterosexual activity with an individual whom they did not consider to be at risk for HIV. These data strongly suggest that many women are unaware of the HIV status of their male sexual partners, particularly when that individual is HIV positive. Contrary to the opinions of many, women who have acquired HIV infection through heterosexual transmission are not more promiscuous or significantly different in life-style from HIV-negative women in their age and ethnic group. Among women who acquired HIV infection through heterosexual transmission in Rhode Island, 70% had been in a long-term, stable relationship with a single partner for at least 2 years, and their median number of sexual partners over the last decade was 3.⁵

All RI women must be offered prenatal testing and education regarding HIV infection, particularly during prenatal care. One recent study determined that if testing had been restricted to women with recognized risk factors, only 57% of HIV-positive women would have been identified.⁶ When HIV testing was offered to all individuals, 87% of infected women were detected.⁶ Therefore, it is vital that physicians extend their attention beyond the stereotypical "high risk" behaviors and consider all women who are sexually active to be at risk for HIV. Early diagnosis of HIV infection is critical to provide women full advantage of antiretroviral therapy and prophylaxis against opportunistic infections.

Natural History of HIV Infection

To investigate the course of immune suppression in HIV-infected women, we

... to study the natural history of HIV infection under conditions of optimal health, the Women's Immunology Center was established ...

retrospectively identified 40 HIV-positive women for whom the date of seroconversion could be determined to within 9 months.⁷ All women were prescribed antiretroviral therapy and prophylaxis according to established guidelines. When analyzed by simple linear regression analysis, the mean decrease of the CD4 lymphocyte count per year was 70 cells/mm. The mean time at which CD4 lymphocyte counts dropped below 500 was 5 years and the average time at which CD4 counts dropped below 200 was 10 years after seroconversion (Figure 2). Both women who acquired the infection through intravenous drug use as well as those who acquired it through heterosexual transmission had the same clinical and immunological course. The data for this small cohort are encouraging because they indicate that the rate of decline of CD4 count from time of seroconversion in women is no greater than in men; indeed it may be less rapid. The route of infection appears to have no influence on the course of HIV infection in women.

Clinical Manifestations & Therapy

Specific clinical conditions may be clues that trigger the consideration of HIV infection in women. In particular, new onset or increased frequency of vaginal candidiasis may occur relatively early in HIV infection. Among a cohort of 117 symptomatic HIV-infected women followed regularly here in Rhode Island,

ABBREVIATIONS USED

AIDS: Acquired immune deficiency syndrome
AZT: Zidovudine
BRUNAP: Brown University AIDS Program
CDC: Centers for Disease Control
ddC: Zalcitabine
ddl: Didanosine
FACTS: Family AIDS Center for Treatment and Support
HER: HIV Epidemiology Research
HIV: Human immunodeficiency virus
PID: Pelvic inflammatory disease
SIL: Squamous intraepithelial lesions
VNA: Visiting Nurse Association



Fig 1.—Percentage of women with HIV infection from heterosexual transmission presenting to the Brown University AIDS Program from 1986 to 1992.

the initial clinical manifestation of HIV infection was new or increased frequency of *Candida* vaginitis in 37% of women. Although HIV-infected women may present to their physicians because of increased frequency of episodes of *Candida* vaginitis, these episodes are often not recognized as being HIV-related.

Other initial clinical manifestations of HIV infection include persistent lymphadenopathy (15%), bacterial pneumonia (15%), acute retroviral syndrome (rash and mononucleosis like syndrome) (7%), and constitutional symptoms such as weight loss and diarrhea (7%).⁴ Pelvic

inflammatory disease, increasingly frequent or severe mucosal herpetic infections, cervical dysplasia, and other sexually transmitted diseases, should also lead the physician to offer HIV testing and counseling (Table 1).

Antiretroviral therapy with zidovudine is equally effective in women and men.⁸ Although the numbers of women were relatively small, the data from the AIDS Clinical Trial Group Study of AZT demonstrated no difference in the benefits or the toxicity of AZT for women as compared to men. Guidelines for the administration of AZT, ddI and ddC ther-

apy are identical in women and men.

When CD4 lymphocyte counts drop below 200, *Pneumocystis carinii* pneumonia prophylaxis should be initiated. Both oral trimethoprim-sulfamethoxazole or dapsone are superior to prophylaxis with aerosolized pentamidine. In our experience, both bactrim and dapsone are tolerated extremely well with an apparently lower incidence of allergic reactions in women than that observed in HIV-infected homosexual men.

In women as in men, it is very uncommon for severe opportunistic infection to occur when the CD4 lymphocyte count is above 200. However, the distribution of AIDS-defined diagnoses is different in women than in men. Nationwide data indicate that *Candida* esophagitis is nearly twice as likely to be the AIDS-defining illness in women (25%) as in men (13%). However, the manifestations of esophageal candidiasis are similar in women and in men (Table 2).

Kaposi's sarcoma occurs much less frequently in HIV-infected women than in homosexual men. In those rare instances when Kaposi's sarcoma has been diagnosed in women, it has often been associated with sex with a bisexual man. *Pneumocystis carinii* pneumonia is becoming increasingly less frequent with

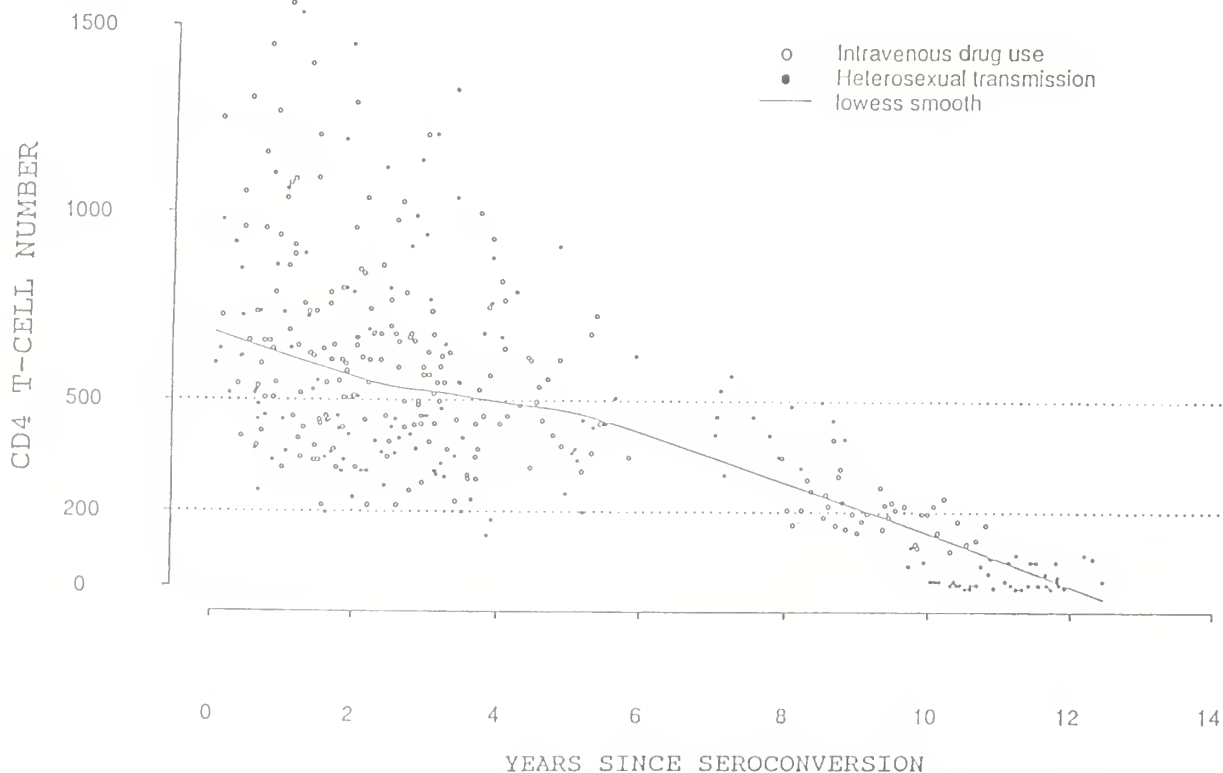
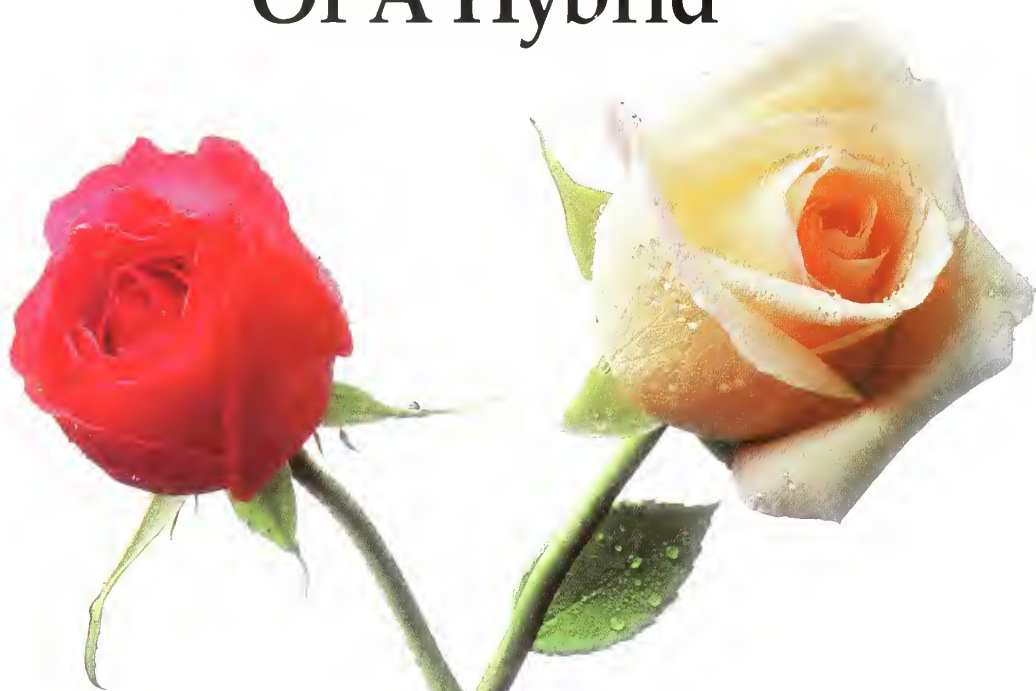


Fig 2.—Serial CD4 T-cell numbers over time since seroconversion for 40 HIV-positive women in Rhode Island. All CD4 counts plotted as a function of time after date of seroconversion. A lowess smooth curve was fitted to the data. Individuals who acquired the infection through heterosexual transmission are depicted in black.

Discover The Elegance Of A Hybrid



At first glance, it's the *beauty* of a rose that catches the eye. The vibrant color. The delicately shaped petals. But study it more closely, and its *elegance* becomes apparent—a gentle blend of softness and strength.

At first glance, it's the *enhanced performance* of Vaseretic that catches the eye. But study Vaseretic more closely, and its *elegance* becomes apparent. The way its one-tablet, once-a-day dosage minimizes multiple

medications. Minimizes insurance copayments. And minimizes potassium supplementation.

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And an elegant discovery for your practice.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

VASERETIC® 10-25
Enalapril Maleate-Hydrochlorothiazide

Next

Dosage must be individualized, the fixed combination is not for initial therapy.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, see adjacent pages.

TABLETS **VASERETIC** (ENALAPRIL MALATE HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC (Enalapril Malate Hydrochlorothiazide) should be discontinued as soon as possible. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality)

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: General. *Enalapril Malate, Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided. (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Enalapril Malate and Hydrochlorothiazide).

Pregnancy, Enalapril Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses, 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible (See Enalapril Malate, Fetal/Neonatal Morbidity and Mortality, below.)

Enalapril Malate, Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no

10
mg



25
mg

alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intrauterine environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contractions stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used were up to 337 times (in rats), and 50 times (in rabbits) the maximum recommended human dose. **Hydrochlorothiazide, Teratogenic Effects:** Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4-56 mg/kg/day (approximately 1-2 times the usual daily human dose) did not impact fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Neonatal Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: General. *Enalapril Malate, Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dose reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See Drug Interactions.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see Drug Interactions, Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment except in extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the

treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather, appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypernatremia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postmyopathic patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium, thus may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients, Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions, Enalapril Malate, Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (See WARNINGS).

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium. **Hydrochlorothiazide:** When administered concurrently the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates, or narcotics: potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin):—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs:—additive effect or potentiation.

Cholestyramine and colestipol resins:—Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. Thiazides may be administered two to four hours before the resin when the two drugs are used concomitantly.

Corticosteroids, ACTH:—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine):—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine):—possible increased responsiveness to the muscle relaxant.

Lithium:—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs:—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse

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YOCON®

YOHIMBINE HCl

bone marrow assay

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: reverse mutation assay with *E. coli* sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 475 to 1300 µg/ml, and in the *Aspergillus nidulans* non-disjunction assay, at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy, Prenatal/Neonatal Morbidity and Mortality: See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain, *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia, *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth, *Nervous/PSYCHIATRIC:* Insomnia, nervousness, paresthesia, somnolence, vertigo, *Skin:* Pruritus, rash, *Other:* Dyspnea, gout, back pain, arthralgia, diphtheria, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, Cough.

Clinical Laboratory Test Findings, Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate: Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, Hemodialysis Patients), *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension), pulmonary embolism and infarction, pulmonary edema, rhythm disturbances including atrial tachycardia and bradycardia, atrial fibrillation, hypotension, angina pectoris, *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth, *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression, a few cases of hemolysis in patients with G-6-PD deficiency have been reported in which a causal relationship to enalapril cannot be excluded, *Nervous System/PSYCHIATRIC:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dyesthesia), *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecostasia, *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, alopecia, flushing, photosensitivity, *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Hydrochlorothiazide: *Body As A Whole:* Weakness, *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), saladenitis, cramping, gastric irritation, anorexia, *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia, *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions, *Musculoskeletal:* Muscle spasm, *Nervous System/PSYCHIATRIC:* Restlessness, *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS), *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia, *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral alpha-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

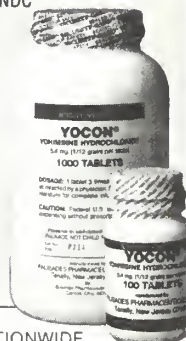
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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appropriate prophylaxis. In a cohort of 135 women followed here in Rhode Island, *Pneumocystis carinii* pneumonia had been recognized in only 5% of those individuals with a mean CD4 count of 50.⁹ Bacterial pneumonia is a common clinical manifestation of HIV infection in women as in men. In fact, community-acquired pneumonia occurred three times more frequently than *Pneumocystis carinii* pneumonia. It is caused by the common respiratory pathogens, usually *Streptococcus pneumoniae* or *Haemophilus influenzae*. The increased incidence of community-acquired pneumonia is not limited to individuals whose CD4 counts are under 200. In our experience, the mean CD4 count among HIV-infected women with community-acquired pneumonia was 240, ie, many presented with higher CD4 counts. Patients with HIV infection and bacterial pneumonia are more likely to be bacteremic than their HIV-negative counterparts. However, the response to prompt administration of appropriate antibacterial therapy in HIV-infected women appears to be good.

HIV-infected women are at increased risk for cervical dysplasia due to human papilloma virus, particularly strains 16 and 18. Advanced cervical neoplasia is associated with declining immune function, measured both by CD4 lymphocyte counts and by HIV stage. Cervical carcinoma is the most serious gynecological condition that occurs with increased frequency in women with HIV infection. In one recent study, 40% of HIV-infected women had abnormal pap smears demonstrating pre-cancerous squamous intraepithelial lesions (high grade SIL) compared to less than 7% of HIV-negative women in the same age group. In our experience in Rhode Island, 44% of women with HIV infection had cervical cytologic abnormalities. Of these, 34% were high grade SIL.¹⁰ Due to the increased incidence of cervical dysplasia, women with HIV infection should have pap smears at 6-month intervals. Conversely, any women with high grade pre-cancerous lesions on pap smear should be encouraged to undergo testing for HIV. Although the increased frequency of high grade SIL in HIV-infected women is well established, it remains controversial

Table 2.—Predictive value of CD4 lymphocyte counts for certain HIV-associated infections and neoplasms in North American women.

CD4 count cells/mm ³ *	Opportunistic infection or neoplasm	Frequency** (%)
>500	Recurrent candida vaginitis	20-40
	Cervical dysplasia/neoplasia	5-40
	Herpes zoster, polydermatomal	5-10
	Bacterial pneumonia	10-15
200-500	<i>M. tuberculosis</i> , pulmonary and extrapulmonary	1-40
	Oral hairy leukoplakia	40-70
	Candida pharyngitis (thrush)	40-70
	Kaposi's sarcoma, mucocutaneous	<1
100-200	<i>Pneumocystis carinii</i> pneumonia	45-70
	Herpes simplex, chronic, ulcerative	10-20
	<i>Histoplasma capsulatum</i> , disseminated	0-25
	Kaposi's sarcoma, visceral	<1
	Progressive multifocal leukoencephalopathy	2-3
	Lymphoma, non-Hodgkin's	2-5
	<i>Cryptosporidium parvum</i> enteritis	2-10
	<i>Mycobacterium avium</i> , disseminated	25-40
<100	<i>Toxoplasma gondii</i> encephalitis	3-15
	<i>Cryptococcus neoformans</i> encephalitis	3-10
	<i>Candida albicans</i> esophagitis	15-20
	CMV, focal and/or disseminated	25-40
	Lymphoma, CNS	1-3

* Table indicates CD4 count at which specific infections/neoplasms generally begin to appear. Recurrence of each infection may occur at any subsequent time in the course of infection.

** Even within US, great regional differences in incidence of specific OIs is apparent. For example, disseminated histoplasmosis is common in the Mississippi River drainage area, but very rare in individuals who have lived exclusively on the East or West Coast.

whether there is a more rapid progression to cervical carcinoma. Prospective studies are now under way that should clarify the incidence of pre-cancerous cervical lesions and the course of cervical neoplasia in HIV-infected women.

Other sexually transmitted diseases are common in the setting of HIV infection. The most common gynecological infections reported among HIV seropositive women are vaginal candidiasis, bacterial vaginosis, and trichomoniasis. Even in individuals with depressed CD4 counts, *Candida* vaginitis generally responds well to topical antifungal agents. Although infections may recur frequently, each episode responds rapidly to standard therapy. Trichomoniasis and bacterial vaginosis are also common in this patient population and are diagnosed and treated no differently than in other women.

Among women with HIV infection followed in Rhode Island, the most frequent cause of genital ulcers was *Herpes simplex* virus II infection. Herpetic ulcers are particularly important in both women and men because, besides the pain and discomfort they cause, the breakdown in epithelial integrity may facilitate HIV transmission. Therapy with oral acyclovir (200 mg 5 times a day) is usually adequate. This may be supplemented with acyclovir 5% ointment. In

patients with severe recurrent herpetic infections, it is often appropriate to recommend long-term oral acyclovir prophylaxis (400 mg twice a day). Occasionally, acyclovir resistant strains of *Herpes simplex* develop in immunodeficient patients on long-term acyclovir therapy. In such cases, intravenous foscarnet is highly effective.

Pelvic inflammatory disease (PID) appears to be frequent in patients with HIV. The presentation symptoms of PID may be subtle. Cervical motion tenderness, which is considered a classic manifestation of PID, may be only minimal. HIV-infected women were more likely to have tubo-ovarian abscesses. In one study, HIV-infected women required surgical intervention more frequently than HIV-negative women with PID. Prospective studies are needed to find whether the high incidence of PID is related to HIV-related immunodeficiency.

Before 1988, several studies had suggested that women with HIV infection had a clinical course that progressed more rapidly than men and that women with CDC-defined AIDS had a shorter survival than men. However, studies at Brown University indicated that HIV-infected women generally had less access to medical care than men for multiple reasons. Most women with HIV infection have

Table 1.—Gender-related Manifestations of HIV Infection in Women.

1. Recurrent vaginal candidiasis
2. Extensive chronic perineal ulcers, 2° to HSV-2
3. Cervical dysplasia/neoplasia

dependent children, and they often placed a higher value on the medical care of their children than on their own health care. Most were economically disadvantaged and many were single parents. For many of the women their medical care was fragmented, with general medical care provided at one site, gynecological care at another site and sometimes obstetrical care at a third site, resulting in an impaired recognition of the full spectrum of HIV in women.

The Women's Immunology Center

To improve health care access for women with HIV infection and related immune disorders and to study the natural history of HIV infection under conditions of optimal health care, the Women's Immunology Center was established in the Fain Health Centers of The Miriam Hospital in early 1990. Two general internists, two infectious disease specialists, one full-time gynecologist, two psychiatrists, and two full-time nurse specialists staff the center and use a multidisciplinary approach for the care of women with HIV infection.

The results to date have been gratifying. More than 300 women with HIV infection have visited the Women's Immunology Center more than 2000 times in 1992. Fewer than 5% of patients have been lost to follow-up since the center was established, in part due to the multidisciplinary approach to care and to the assistance provided to women for travel expenses and child-care during visits when needed.

A weekly conference of community agency representatives on issues relevant to the care of patients with HIV has been integral to the provision of multidisciplinary care. Along with Immunology Center staff, representatives of Rhode Island Project AIDS, Family AIDS Center for Treatment and Support (FACTS), Family Services of Rhode Island, Hospice Care of Rhode Island and VNA Hospice Care, and Sunrise Community Housing attend the meetings, providing an important contribution to the care of women with HIV infection. They have been particularly critical in providing home care to very ill patients, enabling many of these women, most of whom have dependent children, to remain at home throughout entire course of their illness.

The Women's Immunology Center, as part of the Brown University AIDS Program (BRUNAP), has become one of four national sites selected for a long-

term CDC-supported study of the natural history of HIV infection in American women. (The other sites are the Johns Hopkins Hospital, the Montefiore Medical Center in New York, and the Wayne State University Hospital in Detroit.) The primary purpose of this HIV Epidemiology Research (HER) study is to identify those features of HIV infection of greatest significance to women and to provide the best possible therapy for these conditions. The study is also designed to determine whether there are significant gender differences in response to antiretroviral drugs and other medications used to treat the conditions associated with immunodeficiency. The Brown University AIDS Program will enroll 200 HIV-positive women and 100 HIV-negative women in Rhode Island and Southeastern Massachusetts as part of the HER study. Interested individuals can call 274-HERS and ask for Frances Bettencourt, RN to learn more about the study.

Social Impact of HIV Infection

The epidemic of HIV infection has been superimposed on a background of a nationwide epidemic of drug abuse. Besides the well-described role of needle-sharing by intravenous drug users in HIV transmission, crack cocaine use has greatly facilitated the heterosexual transmission of HIV infection. In one study among pregnant rural women who acknowledged crack cocaine use but denied intravenous drug use, the incidence of HIV infection rate was over 30%. In conjunction with medical care, drug abuse counselling and treatment is critical. Often this involves using multiple resources in the community, including both inpatient and outpatient drug treatment programs as well as methadone maintenance and self-help programs such as Narcotics Anonymous and Alcoholics Anonymous. In particular, pregnancy may provide a motivation for many women to seek both medical care and drug treatment.

The social implications of HIV infection in women are significant and complex. Most HIV-positive North American women are mothers with dependent children and are the primary caregivers in their family. Of foremost concern to many of these women is the knowledge that they may be unable to carry out the traditional role of care-giver for their children. The primary motivation for women to seek medical care and for strict compliance is often concern for their dependent families.

The majority of American women

with HIV infection live in urban areas, are poor and are members of minority groups. These women traditionally have had great difficulty in gaining access to appropriate health care. They suffer under the burden of a chronic and ultimately lethal disease, severe economic hardship, and often the sole responsibility to care for their families. Besides medical care, social support must be provided for these women and their dependent children. Thus, a wide array of health care workers, social service and mental health professionals needs to be trained to understand the complex set of issues posed by the expansion of the AIDS epidemic among women, and need to be trained to work together effectively with a comprehensive and multidisciplinary approach.

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Essentials of Pediatric AIDS

Peter S. Smith, MD

In the past decade pediatric HIV infection has become a major worldwide scourge of childhood, the impact of which will be devastating for years to come. Because the overwhelming number of cases occurs in offspring of women who may not know they are infected, and since there is no vaccine available, prevention relies entirely on behavioral change. Since no cure of the disease is in sight, the number of mothers and children with AIDS will continue to increase.

Transmission

The risk of perinatal transmission has been reported to range from 13% to 60%.¹ Most studies support an intermediate acquisition rate of HIV infection of approximately 30%. The transmission rate tends to be higher in mothers who have already given birth to an infant who developed HIV infection or who themselves were symptomatic when they delivered. Beyond any doubt, breast-feeding is an independent risk factor.² This places infants in tropical countries in a poignant dilemma since infants' risk of fatal diarrheal diseases from bacterially contaminated water used in artificial formulas is greater, perhaps outweighing the risk of acquiring HIV infection through nursing.

Epidemiology

The number of HIV-infected women and children in the world is estimated to have reached about 500,000 by the end of the first decade of the pandemic.³ It is thought that the global number of HIV-infected women in 1992 was 4 million and children, 1 million. By early 1990 more than 3 million women, most of child-bearing age and about 80% from

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sub-Saharan Africa were infected with HIV. AIDS will kill 3 million more people in the 1990s, according to the World Health Organization.³ The HIV seroprevalence per 100,000 women aged 15 to 49 varies from 2500 in sub-Saharan Africa to 5 in Eastern Europe. The incidence of HIV infection in other developing countries is accelerating. The prevailing pattern of transmission is heterosexual intercourse, which is increasingly seen in the developed world where it is expected to surpass that recorded among gay men. In such industrialized and wealthy nations a few cases occurred in infants transfused with HIV-contaminated blood and in children with severe hemophilia who were infected with concentrates of clotting proteins harvested from large donor pools. Such infection transmission modes have disappeared with preventive measures in collection of blood and blood fractionation products. Among individuals with hemophilia, no cases have occurred in previously untransfused persons since 1985.

In the US, the Centers for Disease Control and Prevention have received reports of 242,146 cases of AIDS through September 1992. Of those, 4051 were children between birth and 12 years of age. Another 912 cases were among adolescents 13 to 19-years-old. The number of new cases had increased by 48% since 1989. Over half of the cases had died, and most were seen in African-Americans (50%) and Hispanics (24%). The vast majority of cases are by perinatal transplacental transmission.

The impact of AIDS on the pediatric population is not limited to acquisition of HIV. As a result of parental infection, it is expected that by the end of 1995 there will be 18,500 children orphaned by AIDS. Seventy percent of these infants' mothers have either used intravenous drugs or have had sex with an intravenous drug user. Several reports underline the frequency with which women were unaware that their partner was infected. An ongoing population-based serological survey of child-bearing women has measured the maternal HIV antibody in

From 1989 through 1992, 48 cases of HIV infection were reported to the Health Department in children younger than 12 years of age and 7 in children with hemophilia between 13 and 19 years of age.

anonymous heel-stick blood samples of infants born in a variety of hospitals in the United States. Based on this surveillance study conducted in 44 states, neonatal HIV seroprevalence varies from less than 0.1% in most states to as high as 1.25% in New York City, 0.97% in Washington, DC and 0.49% in New Jersey. The national average is 0.15%. This would result in 1600 to 1800 infants born with HIV infection each year if one assumes that about a third of seropositive infants are truly infected. In a study conducted through the Centers for Disease Control and the Pediatric Spectrum of Disease Clinical Consortium, 56% of the 1683 children enrolled in the study by the end of 1990 were living with a biologic parent, 10% with a relative and 27% were in foster care. Only 3% were adopted.⁴

In Rhode Island, 48 cases of HIV infection were reported from 1989 through 1992 to the Health Department in children younger than 12 and 7 in children with hemophilia aged 13 to 19. Rhode Island requires that HIV testing be offered by health care professionals to women attending prenatal, family planning and STD clinics. Rhode Island was also one of the states participating in the anonymous seroprevalence study of the Centers for Disease Control. This enabled us to ascertain the proportion of children referred to the state's only pediatric HIV clinic at Rhode Island Hospital. In 1991, there were 20 anonymous heel-stick HIV-positive infants. During the same time 16 HIV positive infants were

ABBREVIATIONS USED

AIDS: Acquired immune deficiency syndrome

ARC: AIDS-related complex

CDC: Centers for Disease Control

ddl: Didanosine

FACTS: Family AIDS Center for Treatment and Support

IgA: Immune globulin A

IgG: Immune globulin G

PCP: Pneumocystis carinii pneumonia

PCR: Polymerase chain reaction

ZVD: Zidovudine

referred to the Pedi II clinic (our clinic for HIV positive children), presumably most of them from the anonymous HIV positive pool. In 1992 there were 27 seropositive infants (a seroprevalence of 0.18%) and 14 new infants attended the Pedi II clinic. This suggests that the numbers of HIV-positive infants followed in the clinic is somewhere between 50% and 80% of those infants who are HIV-positive and that in the past 2 years there are as yet unidentified children with HIV infection in our midst whose mothers declined testing or delivered without prenatal care.

Clinical Manifestations

HIV expresses itself in a variety of manifestations in children, perhaps because HIV may affect specific organs and host immunity more profoundly before they are fully differentiated. The clinical presentation of pediatric HIV infection also varies with age. For example, interstitial lymphocytic pneumonitis and parotitis, which are more indolent and chronic than pulmonary opportunistic infections, tend to be seen more often in older children, whereas a failure to thrive syndrome is more common in infants. AIDS-defining opportunistic infections can occur at any age, but in most perinatally acquired infections they occur predominantly in the first years of life.^{5,6}

Systemic Manifestations

Failure to thrive.—Failure to gain weight, height and to reach the expected milestones of development are the predominant presentation in AIDS children. The onset may be quite subtle, usually beginning with a flattening out of the weight curve, which may show the crossing of one or more percentile lines without any other symptoms. Developmental achievements in language, movement, and behavior may not be reached at the expected time, or the mother may observe that her child progresses more slowly than another sibling. Arrest of linear growth or in head growth generally occurs in more advanced stages of HIV infection.

Generalized lymphadenopathy and splenomegaly.—While enlargement of cervical lymph nodes is commonplace in the first several years of life, particularly with infections of the upper airway, it is unusual for a child to have palpable axillary and inguinal lymph nodes. When this happens the spleen is usually also palpable a few centimeters below the costal margin.

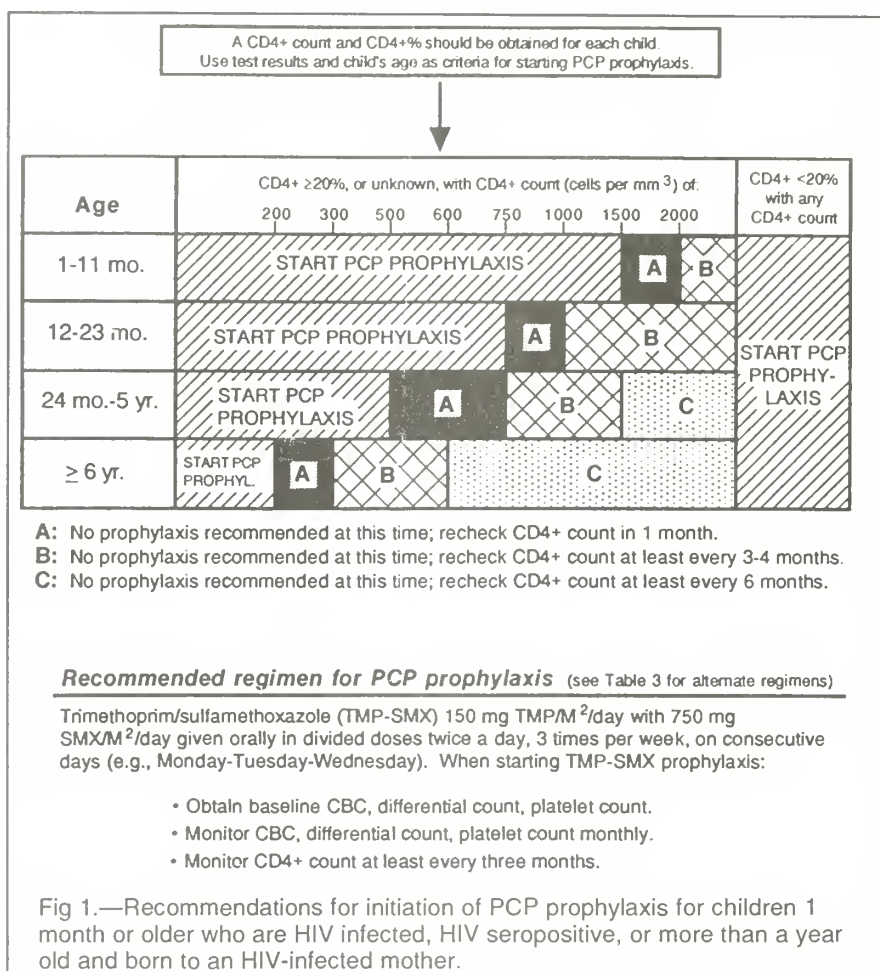


Fig 1.—Recommendations for initiation of PCP prophylaxis for children 1 month or older who are HIV infected, HIV seropositive, or more than a year old and born to an HIV-infected mother.

Persistent fever and chronic diarrhea.—This may also occur as systemic presenting symptom but are generally associated with other signs and symptoms of disease. For instance fevers lasting over a week are more often associated with chronic infections. Recurrent bacteremia is a consequence of impaired humoral immunity in these children and must be suspected when fever is noted without localizing findings.

Organ-specific Manifestations.

Virtually every organ in the body may be affected by HIV but the most frequently affected target organs in children are:

The blood.—Unlike the adult population, in which frequent bacterial infections are less prominent, children, particularly infants often have one bacterial infection after another, such as pneumonia, cellulitis, chronic otitis media, sinusitis and sepsis, presumably because of an impairment in the response to new antigens. More typically the organisms involved are Gram positive, ie, pneumococci. Older children and adults have already developed an immune response to most bacterial antigens and are less

likely to develop frequent bacterial diseases.

Lungs.—The earliest cases of AIDS-defining illness were in infants who developed respiratory distress from *Pneumocystis carinii* pneumonia (PCP) and remains the most common opportunistic infection in children as it is in adults. The leading cause of mortality in children, *Pneumocystis carinii* pneumonia may have an insidious or acute onset with tachypnea and cough progressing to severe respiratory distress. Fever and cyanosis after bouts of coughing may be noted. The chest X-ray typically shows a diffuse infiltrate that may lag behind the symptoms. The diagnosis is established with appropriate histological stains of bronchial washings, but the presence of diffuse interstitial pneumonia and hypoxia in a child known to be HIV seropositive is sufficient to warrant immediate treatment with specific antimicrobials.

Interstitial lymphocytic pneumonitis occurs in about half of children with AIDS and tends to cause respiratory distress less frequently. Symptoms may develop, however, with progressive disease and require treatment with steroids. The X-ray pattern is similar to that of

PCP but is more reticulonodular. Occasionally a biopsy is required for a definitive diagnosis. The tissue may show infiltration of the septae and peribronchial areas by lymphocytes and plasma cells. The etiology is unknown, although HIV and Epstein-Barr Virus have been hypothesized to be involved in its pathogenesis.

Central Nervous System.—HIV is capable of directly affecting neurons as well as surrounding glial cells. AIDS encephalopathy occurs in a significant number of children. Symptoms range from developmental delays to motor abnormalities such as paraparesis and spasticity. Seizures are rare. Onset of symptoms in the first year of life denotes a particularly bad prognosis.

Heart.—Although cardiomyopathy causing heart failure is not seen frequently in early disease or as a single organ involvement, it is common in end-stage disease. Autopsies performed on children who had AIDS invariably show dilation of the chambers and hypertrophy of the ventricles, as in adults. Even without clinical symptoms of cardiac decompensation, however, echocardiographic abnormalities were found in children in various stages of the disease.⁷ The most frequent abnormalities included evidence of ventricular dysfunction, pericardial effusion and endocarditis.

Gastrointestinal Tract.—Much of the failure to thrive is thought to be from impairment of the gut. The cause is probably multifactorial: anorexia from chronic disease, increased metabolic rate from chronic infection, malabsorption from *giardia* and other infections. The most common infection seen is oropharyngeal candidiasis, which may extend to the esophagus. Other infective agents may cause chronic diarrhea, such as *Salmonella*, *Shigella* or the enteroviruses, but more often no specific agent is identified.

Centers for Disease Control Classification

To clarify the complexity of pediatric AIDS, a panel of consultants convened by the Centers of Disease Control devised a simple scheme.⁸ Although the main purpose was to standardize epidemiologic studies, disease surveillance and prevention programs it also considered the uniqueness of pediatric presentations and that children with HIV infection can succumb to the disease without fulfilling the criteria of the CDC adult AIDS definition. The system also allows clinicians to communicate better with each other,

instead of using non-descript terms such as ARC.

In broad strokes the system defines whether the infant has passed the age when the currently accepted diagnostic HIV antibody test can no longer be explained by transplacentally transferred maternal antibodies. Until age 15 months one refers to stage P₀ or *indeterminate* stage. If before that time the infant becomes symptomatic there are specific criteria to be met to establish that the infant is definitely infected, such as failure to thrive, in the presence of a positive viral culture. In stage P₁ the infant has gone beyond the 15 months threshold but remains asymptomatic. Any child between the ages of 15 months and 13 who has symptoms is in stage P₂. If symptoms are of a generalized nature such as weight loss, lymphadenopathy, or persistent fevers the letter A (ie, P₂A) is added. More letters are added depending on the specific manifestations (eg, P₂B refers to any neurologic abnormalities). One can easily list all the manifestations of pediatric HIV infection if one recalls the letters up to F of the CDC classification. Of clinical importance is that all children in stage P₂ are generally treated.

Laboratory Studies

The gold standard to diagnose HIV infection in neonates is a positive viral culture of the blood, but few can perform or afford such labor intensive methods of diagnosis. One therefore relies on a combination of HIV induced symptoms and laboratory studies.

HIV Specific

Until further notice the mainstay of the diagnosis is the detection of serum antibodies to specific HIV antigens confirmed by a Western blot assay.

Virus Culture.—A positive culture is of particular importance in the ill infant whose symptoms could be ascribed to a primary immune deficiency or another disease causing the same symptoms as HIV.

HIV p24 Antigen.—When present, which is not often, this assay can be useful. It generally denotes an excess of circulating viral core antigens and correlates with progressive deterioration. Recent technical refinements should increase the sensitivity of this assay by dissociating the antigen from immune complexes.

HIV Antibodies.—The viral antigens that are used for the interpretation of the confirmatory, more specific, immunoblot assay include envelope and core pro-

teins. To be considered positive, the Western blot must generally show one envelope band and an additional band, usually the p24 from the core.

Polymerase Chain Reaction.—This highly sensitive assay detects the presence of HIV provirus in circulating lymphocytes by amplifying specific DNA sequences. The main problem with this highly sensitive and specific test is the unacceptably high number of false positive results that can result from minuscule amounts of contaminants. Should the technique be adequately controlled in quality so that reliability were not an issue it would be a significant advance in identifying HIV infection in infants at an early stage. Therefore we would be able to know which infants to monitor more carefully and, if necessary, to treat. However, few would advocate beginning potentially toxic treatment on the strength of a positive PCR only.

Immunology.—The most useful assessment of immune function at the current state of our knowledge consists of determining the T-cell lymphocyte subsets and quantifying the immunoglobulin levels. The CD4 (helper) subset is normally higher in infants than in adults and nomograms are used to determine normal ranges. The same rule as in adults obtains regarding the CD4/CD8 ratio; however, a proportion less than 1 correlates with a greater risk of symptomatic disease and poorer prognosis.

The gamma fraction of the serum immunoglobulins is often elevated in infants with HIV, a result of B-cell hyperactivity. IgA may increase as early as 3 months of age, and IgG levels 3 to 4 times normal may occur well before the critical 15-month turning point has been reached when the persistence of HIV antibody means infection. Immunoglobulins may also be below normal, particularly in infected premature infants.

Management

The Pedi II Clinic for HIV Positive Children in Southeastern New England

Currently 32 children attend this clinic, which is staffed by pediatricians familiar with HIV infection, a nurse coordinator, a nurse educator, a case manager and other professionals such as an infectious disease consultant, as needed. Besides complete physical examinations and developmental assessments, the children have cellular and humoral immunity assessed at regular intervals, chest X-rays if there are pulmonary symptoms and other

imaging studies as indicated. About half the children are symptomatic or have a significant cellular immune deficiency (less than 2 standard deviations below the normal number of T helper lymphocytes, CD4 cells) and receive antiretrovirals such as didanosine (ddI) and zidovudine (ZVD).

Antiretrovirals.—Zidovudine (ZVD) and didanosine (ddI) are the only products currently licensed to be used in HIV-infected children. Both are available in liquid or chewable form, and both have excellent track records. Overall, improvement can be dramatic. It is not unusual to see a wasted hypotonic and apathetic infant within weeks gain weight, become more active and make rapid progress in psychomotor development. One generally starts with 180 mg/m² of ZVD every 6 hours orally and reserves ddI for children who begin to show evidence of clinical or laboratory resistance. Infants and children tolerate both these drugs very well; subjective or even objective side effects are quite unusual.

Prophylaxis to Prevent PCP.—Trimethoprim-sulfamethoxazole is recommended when the CD4 count or percent CD4 drops below an age-related threshold value. A panel convened recently by the Centers for Disease Control and Prevention has published specific recommendations for PCP prophylaxis (see Table 1). Dosage regimens with alternatives for children who cannot take sulfonamides as well as a schema with threshold CD4 counts are published.⁹

Intravenous Gammaglobulin Infusions.—The use of these is controversial, particularly since controlled trials with placebo predated the routine use of ZVD in symptomatic children. Most clinicians would consider its use when a child has had two or more documented serious bacterial infections within a year. There is little reason to withhold antimicrobial treatment in febrile children. Impaired humoral immunity increases their odds of having a serious bacterial infection.

The Family AIDS Center for Treatment and Support (FACTS)

Pediatric HIV infection must be seen within the context of the child's family and environment. Most such children are born to single mothers without skills, a job or resources to handle a child with a significant disability, let alone their own psychosocial, educational and medical

problems. A number of Rhode Island health care providers and community based organizations were aware of the severe overall toll of HIV on families well before the epidemic became increasingly prevalent in the local heterosexual population.

The first child in the area with AIDS was a teenager with hemophilia who was receiving his community-based, coordinated and multidisciplinary care through the Hemophilia Center at Rhode Island Hospital. All the resources required to manage this boy's disease and to make it possible for him to lead as normal a life within his own community were mobilized to good effect. It was a logical step to set up a similar comprehensive approach for infants and their parents in anticipation of a disease likely to strike the socially disenfranchised persons within our own state.

FACTS was founded by the religious team ministry of a parish serving those most likely to be affected, a social worker in the leadership of a major community-based organization and the physician in charge of the Rhode Island Hemophilia Center. The FACTS program reaches out to provide care to all local children and their families struggling with HIV infection. It is directly linked to the Pediatric HIV Clinic at Rhode Island Hospital whose staff provides the medical supervision and management and has formal ties to the medical professionals and facilities who care for the child's parents, as well as to other organizations within the state serving people with HIV infection, drug addiction, learning and skill deficits.

With a residential program based in South Providence, the FACTS house has a nursery for those infants and children whose family is unavailable and transitional housing for families recovering from addiction or who have no home. FACTS emphasizes the importance of preserving the integrity of the family and makes a strong commitment to the affected child. The process is gradual with frequent visits of the biological parents either in the FACTS nursery or in the home of the foster parents. Strong case management, ranging from providing transportation to a clinic to negotiating services through the intricacies of public agencies and developing practical skills of daily living in family members, is the means that have made FACTS a successful model of community-based, family-

centered care locally and nationally.

Future Perspectives

The epidemic of HIV in our community will require that all of us provide continuous, competent and sensitive care to affected individuals. Most of this care can occur in a primary care setting, and there are resources and training programs available through the Brown University AIDS Program (BRUNAP) and the Department of Pediatrics. These are designed to keep the community physicians abreast of therapeutic advances and make it possible to improve survival and the quality of life of HIV-infected people.

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HIV Clinical Trials in Rhode Island

Gail Skowron, MD

The Brown University AIDS Program (BRUNAP) has been committed to providing state-of-the-art care since 1987 to persons infected with HIV in Rhode Island and surrounding areas. Toward this goal, BRUNAP physicians and nurses have offered their patients participation in innovative clinical trials. Starting with a single study in 1989, this program has expanded to 20 clinical trials.

BRUNAP trials are sponsored by pharmaceutical companies and through funded clinical trial networks. Since 1990, BRUNAP has participated as a site in the American Foundation for AIDS Research (AmFAR)-sponsored Community-Based Clinical Trials Network (CBCTN). Providence also has two sites supported by the National Institutes of Health's Division of AIDS Treatment and Research Initiative (DATRI), at the Miriam Hospital and at Roger Williams Hospital.

Site of Action of HIV Therapeutic Agents

HIV replicates within human CD4+ lymphocytes. The complex life cycle of HIV offers many points at which we may inhibit replication (Figure 1). The earliest attempts to inhibit HIV were focused on the reverse transcriptase, a viral-encoded enzyme. This target was particularly attractive since this enzyme does not exist in human cells and viral replication could be selectively inhibited. The first agent to be approved for use against HIV infection, zidovudine (formerly known as azidothymidine or AZT), is a nucleoside analog, which blocks viral replication due to its resemblance to the natural nucleoside, deoxythymidine. Once a nucleoside analog enters the cell and is phosphorylated, it is incorporated into the growing viral DNA strand. Viral replication is inhibited by competition with natural nucleosides (competitive inhibition). In addition, once incorporated, the nucleoside analog's altered struc-

ture prevents further elongation of the DNA strand (chain termination).

Since AZT's licensure, two additional nucleoside analogs have been approved for use. Didanosine (Videx, formerly known as dideoxyinosine or ddI) and zalcitabine (HIVID, formerly dideoxycytidine or ddC) both inhibit viral replication by mechanisms similar to those of AZT. Additional nucleoside analogs have been under study in recent years, including d4T (2',3'-didehydro-3'-deoxythymidine), 3TC (2'-deoxy-3'-thiacytidine), and FLT (fluorothymidine). Non-nucleoside reverse transcriptase inhibitors bind directly to the viral reverse transcriptase and inhibit its function. Compounds currently under study in this category include nevirapine (formerly BI-RG-587), pyridinone (formerly L-697,661), TIBO (tetrahydroimidazobenzodiazepine) derivatives and BHAP (bis (heteroaryl) piperazine) compounds.

Once viral replication has proceeded from a single-stranded RNA to a double-stranded DNA copy of the viral genome, this provirus can enter the nucleus and become integrated into the host cell DNA using the viral enzyme, integrase. Once integrated, the virus may remain dormant with no active viral replication. This latency period may continue until the viral DNA undergoes transcription into viral messenger RNA and viral RNA genome, in response to certain activation signals. The viral messenger RNA is subsequently translated into both structural and regulatory viral proteins. Structural proteins form the protein core and glycoprotein envelope of newly forming viruses. Regulatory proteins influence the rate of transcription and translation of viral DNA and RNA, respectively. Viral-encoded regulatory proteins, such as *tat* and *rev*, and the protease which cleaves the viral polypeptide chain into active protein fragments, are also targets of antiretroviral therapy.

Thousands of candidate compounds have been tested *in vitro* for activity against HIV. Many compounds are active against a variety of clinical HIV isolates and combinations of two or more agents may exhibit synergistic antiretroviral activity. Two or more compounds may be given concurrently or in a se-

The BRUNAP Clinical Trials Program will continue to offer innovative, new therapies to HIV-infected persons in the Rhode Island area.

quential or alternating manner.^{1,2} Some combinations, such as AZT and alpha interferon, are strategically designed to inhibit the virus at two points in its life cycle.³ In contrast, recent attention has been focused on the concept of "convergent therapy," in which three compounds targeted at a single viral function, eg, reverse transcription, exhibit potent and long-lasting antiretroviral activity.⁴

Immunomodulators and Immunorestitution

Studies are also underway to evaluate various therapies that enhance the function of the immune system (Table 1). These may be directed at replacing low levels of thymic hormones, or increasing

ABBREVIATIONS USED

AIDS: Acquired immune deficiency syndrome

AmFAR: American Foundation for AIDS Research

AZT: Zidovudine

BETA: Bulletin of Experimental Treatments for AIDS

BHAP: Bis(heteroaryl)piperazine

BRUNAP: Brown University AIDS Program

CBCTN: Community-Based Clinical Trials Network

CPCRA: Terry Beirn Community Program for Clinical Research on AIDS

CRINE: Community Research Initiative of New England

DATRI: Division of AIDS Treatment and Research Initiative

d4T: 2',3'-didehydro-3'-deoxythymidine

ddC: Zalcitabine or HIVID

ddI: Dideoxyinosine or videx

DNA: Deoxyribose nucleic acid

FLT: Fluorothymidine

HER: HIV Epidemiology Research

HIV: Human immunodeficiency virus

ODB: Observational Database

OTC: L-2-oxothiazolidine-4-carboxylate or procysteine

THF: Thymic humoral factor

3TC: 2'-deoxy-3'-thiacytidine

TIBO: Tetrahydroimidazobenzodiazepine

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levels of certain interferons and interleukins. Alternatively, a restoration of immune function can be attempted by lymphocyte transfusion or bone marrow transplantation.

Therapies Against Opportunistic Infections

Other therapies are directed against the organisms which cause opportunistic infections, and which are responsible for the majority of the morbidity and mortality associated with AIDS. In recent years, many promising compounds have been tested and shown to be active against the major pathogens in HIV infection.

The Clinical Trials Program

BRUNAP now offers 20 clinical trials. Table 2 lists a brief description of each trial and who to contact for more information.

Antiretroviral Agents

d4T (stavudine).—The first BRUNAP trial in 1989 enrolled 40 participants into a phase I trial of d4T. The first dose of d4T given to humans was administered in Rhode Island as part of this trial. The study demonstrated the beneficial effects of d4T to be elevation of CD4 count, inhibition of p24 antigen, and weight gain.⁵ A second study of d4T, in individuals with hematologic intolerance to AZT, showed that d4T's beneficial effects extended to this population without causing hematologic toxicity. Some participants in these early trials continue to receive d4T in an expanded access program.

3TC (lamivudine).—The newest nucleoside analog to be studied within BRUNAP is 3TC. 3TC is an analog of cytidine, which inhibits HIV via mechanisms similar to those of other nucleoside analogs. Two studies of 3TC are currently open for enrollment in Rhode Island. The first is evaluating the pharmacokinetics of 3TC, AZT and the combination, in individuals with HIV infection. This study involves four short hospital stays to determine whether AZT and 3TC interact when they are administered together.

The second study is part of a multicenter, nationwide study comparing 3TC plus AZT to AZT alone and 3TC alone, in patients with HIV who have not received prior therapy with nucleoside analogs.

AZT for Acute HIV Infection.—With increasing evidence that HIV infec-

Table 1.—Immunomodulators Under Investigation

Alpha Interferon
Autologous CD8 lymphocyte infusions
Bone Marrow Transplantation
Histamine H2-receptor antagonists (cimetidine, ranitidine)
Diethyldithiocarbamate (DTC, dithiocarb, Imuthiol)
Interleukin-2/ Polyethylene glycol-derivatized IL-2
Intravenous Immune Globulin (IVIg)
Lentinan (extract of shitake mushroom)
Thymic humoral factor (THF)
Thymopentin (TP-5)

tion progresses despite the lack of clinical symptoms, the question arose concerning AZT's potential benefit at the earliest signs of infection. A study in progress will identify individuals with symptoms of acute HIV infection (fever, rash, headache, aseptic meningitis) who are presenting for medical care. During this time ("seroconversion") HIV antibody tests are negative, but a p24 antigen test is positive. This study will evaluate the use of AZT in slowing the progression of HIV disease when initiated during seroconversion.

Non-nucleoside Reverse Transcriptase Inhibitors.—The earliest studies of these compounds showed that they possessed potent antiretroviral effects. At the initial doses tested, however, resistance to these agents, and the reemergence of viral replication, appeared after only a few weeks of therapy. Initial enthusiasm was replaced by skepticism about the future utility of this class of drug. Since that time, research has been concentrated on the use of these drugs at higher doses and in combination with other inhibitors of the reverse transcriptase. Combinations of these drugs with AZT and, more recently with both AZT and ddI, showed greater antiretroviral effects than any single drug or two-drug combination.⁴ A BRUNAP study of one of these agents, pyridinone (L-697,661), has recently opened. This study will compare zidovudine plus pyridinone to zidovudine alone for 6 months.

Procysteine.—Procysteine (L-2-oxothiazolidine-4-carboxylate or OTC), is a prodrug of cysteine that increases intracellular concentrations of glutathione. Glutathione is an antioxidant, which acts to remove toxins from the blood. Levels of glutathione are reduced in individuals with HIV infection, partic-

ularly in AIDS, and repletion of glutathione appears to reduce HIV replication. Procysteine increased the levels of glutathione by providing cysteine, which is the rate-limiting component in the formation of the triamino acid, glutathione. BRUNAP has studied Procysteine since 1991 when we participated in the first trials of intravenous Procysteine for HIV infection. Subsequently, an oral form of Procysteine was tested. These early safety studies showed Procysteine to be safe and indicated that CD4+ cell count and glutathione levels rose in response to therapy.

Procysteine has recently entered phase II testing in BRUNAP and 11 other centers across the United States. Participants are randomized to receive one of two dosages of Procysteine or placebo, and may continue on AZT, ddI, or a combination of AZT/ddI or AZT/ddC.

Immunomodulating Agents

Thymic Humoral Factor.—The thymus gland is the site where nacent T lymphocytes are "educated." In HIV infection, the hormonally active thymic epithelium is replaced with scar tissue. In the face of a viral infection that destroys T lymphocytes, therefore, the thymus gland is unable to educate newly formed T cells to become active in fighting the viral infection. Based on these observations, BRUNAP began to study thymic humoral factor (THF) in 1990. A synthetic octapeptide, THF is identical in structure to a naturally occurring thymic hormone. Four dosage levels, 5, 10, 25, and 50 nanograms per kilogram, have been completed. At the highest doses tested, laboratory measurements of immune function improved and skin test reactions were enhanced. Further testing, with intensive laboratory monitoring of HIV-specific immune responses, is currently underway at a dose level of 500 nanograms per kilogram. No significant side effects have been noted. THF is administered once daily as an intramuscular injection; 2 weeks of THF are followed by a 1-week rest period, and these 3-week cycles are repeated four times for a total of 3 months of therapy.

Agents for Opportunistic Infections

In addition to therapies that directly inhibit HIV itself, BRUNAP has embarked upon several trials that study agents active against the opportunistic infections that affect patients with HIV.

Fluconazole for Candida.—This

Steps in Viral Replication

1. Attachment
2. Uncoating
3. Reverse Transcription
4. DNA Synthesis of Second Strand
5. Integration and Latency
6. Viral Transcription
7. Protein Synthesis
8. Protein Glycosylation
9. RNA Packaging and Virion Assembly
10. Release of Virus
11. Maturation

Identified Therapies

1. Soluble CD4, Monoclonal Antibodies
2. Hypericin
3. AZT, ddC, ddI, d4T, 3TC, pyridinone, nevirapine, TIBO, BHAP, Foscarnet
4. None
5. None
6. TAT antagonist
7. Ribozymes
8. N-Butyl DNJ
9. Myristic Acid Analogs
10. Interferon Alpha
11. Protease Inhibitors

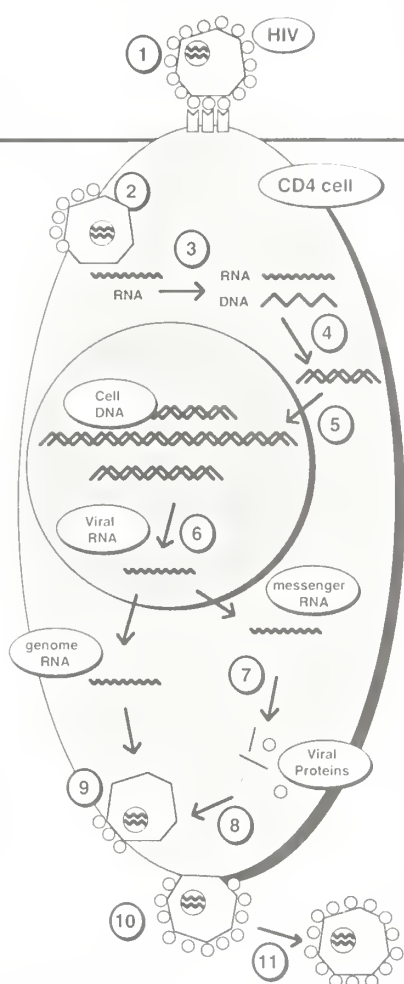


Illustration by Bill Jesdale, Brown University AIDS Program

Fig 1.—Steps in HIV replication and identified therapies. Figure adapted with permission from Nava Sarver, NIAID, *Science* magazine.

study evaluates the ability of fluconazole to prevent recurrence of thrush and candidal vaginitis in women with HIV infection and with fewer than 500 CD4 cells/mm³. Participants are randomized to receive either fluconazole 50 milligrams three times a week or intensive monitoring for the presence of fungal infection. Women not receiving fluconazole who experience recurrent fungal infections are also placed on fluconazole. Preliminary results from this study suggests that fluconazole is indeed active in prophylaxis of mucosal candidal infections.

Paromomycin for Cryptosporidiosis.—Chronic diarrhea in HIV infection is a cause of discomfort, malnutrition and wasting. A severe form of chronic, watery diarrhea is caused by the intestinal parasite, *Cryptosporidium parvum*. A study is now underway to evaluate the effectiveness of paromomycin, also known as Humatin, to treat diarrhea due to this organism.

256U87 for Herpes simplex.—

256U87 is a pro-drug of acyclovir that is rapidly converted to acyclovir after oral administration; its antiviral spectrum is, therefore, the same as acyclovir. In an animal model, mean peak levels of acyclovir after oral 256U87 are nearly 5-fold higher than that achieved from oral acyclovir. This study will compare standard therapy with acyclovir to 256U87 in HIV+ patients with recurrent genital or perianal herpes.

882C87 for Herpes zoster.—882C87 is a new antiviral agent which is three to seven times more potent than acyclovir against *Varicella zoster* virus *in vitro*. This study will compare standard therapy with acyclovir to the new drug 882C87 in HIV+ adults with a new shingles rash (less than 3 days old).

Pharmacokinetic Studies

BRUNAP also collaborates with the University of Rhode Island Anti-infective Pharmacology Research Unit on the

metabolism and distribution of various agents used in HIV infection.

Megace.—Megestrol acetate (Megace) is a synthetic hormone that can induce adipocyte differentiation of fibroblasts and increases cellular metabolism. It is used to promote weight gain in HIV infection. A study to evaluate the pharmacokinetics of Megace was completed in 1990. The study enrolled 10 men with involuntary weight loss. Megace was administered for 21 days as a suspension rather than the currently available pill. All patients reported an increase in appetite and eight gained weight by 3 weeks.

Megace versus Dronabinol.—A second pharmacokinetic study currently open for enrollment compares Megace, Dronabinol and the combination for the treatment of HIV wasting syndrome. Dronabinol, (tetrahydrocannabinol, THC, Marinol), is the active ingredient in marijuana, and has been used in cancer patients to relieve nausea. Dronabinol acts centrally and may stimulate the hunger center in the hypothalamus. Megace and Dronabinol will be compared for their effect on promoting increased appetite and weight gain.

Liver Function Study for Men.—It has been noted that patients with HIV infection are frequently intolerant of other drugs used to treat various symptoms and complications of HIV infection, and thus may require lower doses of drugs. This study is examining the hepatic metabolism of three "model substrate" compounds (antipyrine, lorazepam and indocyanine green) that measure different metabolic pathways in the liver. These three drugs are given before the initiation of zidovudine and is repeated after 4 to 6 weeks to see if antiviral therapy produces changes in hepatic metabolism and if these changes can be correlated to zidovudine metabolism.

Pediatric Studies

Studies in the pediatric population are conducted under Dr Peter Smith of Rhode Island Hospital. Dr Smith heads a satellite AIDS Clinical Trials Unit for the pediatrics service. The ACTU currently offers four protocols for pediatric patients, including one for pregnant women.

AZT versus ddI (ACTG 152).—This study is designed to evaluate the safety and efficacy of monotherapy versus combination therapy in HIV-infected children between the ages of 3 months and 18 years. Children may be enrolled in this study if they have not received antiretro-

Table 2.—Open BRUNAP Clinical Trials

Description	Eligibility	Sponsor	Duration	Design	Contact
3TC vs AZT vs 3TC/AZT	CD4 200-500 AZT naive (<4 wks)	Glaxo	32 weeks	Phase III, double-blind, randomized 3TC 300mg + placebo AZT 200mg + placebo 3TC 150mg + AZT 200mg 3TC 300mg + AZT 200mg Compensation	729-2918 Frances Bettencourt, RN
3TC pharmacokinetics	CD4 > 200 asymptomatic not currently receiving antivirals & ZDV <1 yr.	Glaxo	2 months	4 treatment arms: AZT, 3TC alone & combination of the two. Cross-over to determine if drugs effect the absorption or excre- tion of the other; compensation	456-6592 Mike Dudley, PharmD
Pyridinone (L-667,661)	CD4 < 250	Merck	6 months	Pyridinone/AZT vs AZT	331-8500 x4028 Joan Gormley, RN
AZT for acute HIV Infection	Acute retroviral syndrome	DATRI (NIAID)	6 months	AZT vs placebo	331-8500 x4028 Terry Fiore, LPN
Oral Procysteine Phase II	AIDS/ARC, CD4 50-300 Asymptomatic/AIDS-KS CD4 50-200; taking AZT, ddI, AZT/ddC or AZT/ddI	Free Radical Sciences (Clintec/Baxter)	6 months	2 doses of Procysteine vs placebo. One 8-hour pharma- cokinetic study. Compensation	456-AIDS Grace Accetta, RN
Thymic Humoral Factor (THF) and AZT	CD4 100-500	Adria	5 months	Five dose levels (5,10,25, 50, 500 ng/kg/d) Intramuscular injection daily for 2 wks then 1 week off. Four cycles in total.	456-AIDS Grace Accetta, RN
Fluconazole to Prevent Candidiasis in Women	CD4 <300 prophylaxis vs Rx of acute episodes	AmFAR	2 years	Randomized to fluconazole 50mg 3x/wk or intensive monitoring	274-HERS Terry Fiore, LPN
Paromomycin for Cryptosporidiosis	CD4 <200 with docu- mented cryptosporidia	AmFAR	1 year	Open-label, 500 mg QID for 4 weeks	331-8500 x4028 Terry Fiore, LPN
256U87 vs Acyclovir for recurrent Ano- Genital Herpes	CD4 ≥ 100 with recurrent ano-genital HSV	Burroughs Wellcome	10 days (48 wk extension)	Randomized to 256U87 or Acyclovir; Compensation	456-2215 Lisa Crandall
882C87 vs Acyclovir for Treatment of Shingles	Shingles Rash (Herpes zoster) within 72 hours of onset	Burroughs Wellcome	28 days	Double-blind, randomized to 882C87 or Acyclovir for 4 wks Compensation	781-2400 Lynn Haughey, RN
Megesterol & Dronabinol alone or in combination for HIV wasting syndrome	Loss of 10% body weight currently losing weight Compensation	DATRI (NIAID)	12 wks	Randomization to Megesterol, Dronabinol or combination	456-6592 Sandra Geletko, PharmD
Liver Function Study for Men	CD4 100-500 no antiretrovirals no history of liver abnormalities	AmFAR	4-6 wks	Before & 4-6 weeks after anti- retroviral therapy started, model substrate drugs are given to see if there are changes in liver metabolism; Compensation	456-6592 Michael Dudley, PharmD.
Pediatric AZT vs ddI (ACTG 152)	Children aged 3 mo-18 yrs. Less than 6 wks prior antiretroviral therapy	NIAID	2 years	3 arms: AZT + placebo ddI + placebo AZT + ddI	444-5171 Peter Smith, MD Cathy Kneut, RN
AZT to Prevent Perinatal Transmission (ACTG 076)	Pregnant women not on an antiretroviral	NIAID	2 years	AZT or placebo given to mother and infant	444-5171 Peter Smith, MD Cathy Kneut, RN
Pediatric AZT/ddC Combination (ACTG 190)	Children aged 3 mos. to 12 years, tolerating AZT therapy	NIAID	2 years	Double-blind, randomized to AZT/ placebo or AZT/ddC	444-5171 Peter Smith, MD Cathy Kneut, RN
AZT for Asymptomatic Infants (ACTG 180)	Infants ≤ 9 months of age	NIAID	2 years	Double-blind, randomized to AZT or placebo	444-5171 Peter Smith, MD Cathy Kneut, RN
Vertical Transmission	HIV+ pregnant women, at any time in pregnancy	NIAID	1 year	Donation of several tubes of blood each trimester; collection of cord blood; testing of infant at birth, 2, and 6 months	456-AIDS Gail Skowron, MD Grace Accetta, RN
Observational Database (ODB)	Any HIV+ individual	AmFAR	Open	Anonymous collection of data	456-AIDS
Natural History of HIV Infection in Women (HER Study)	IIIV-infected women with CD4 >200; HIV-infected women at high risk	CDC	5 years	Interviews, physical exams and laboratory assessments Compensation	274-HERS Frances Bettencourt, RN
AIDS Immunology Study	Asymptomatic with CD4 >400; Long-term survivors	California Community Foundation	Open	Donation of several tubes of blood every 2-6 mo. for 1-2 years	456-AIDS

viral agents or have received less than 6 weeks of prior drug therapy. Children will be randomized to one of three treatment arms: AZT plus placebo, ddI plus placebo, or AZT plus ddI.

AZT in HIV-Infected Pregnant Women (ACTG 076).—This study is designed to evaluate the use of AZT during pregnancy to prevent the vertical transmission of HIV from an infected mother to her infant. HIV-infected pregnant women who are not receiving AZT for their own infection are eligible to participate in this study. Participants will be randomized to receive either AZT or placebo during pregnancy and during labor and delivery. Infants born to HIV-infected mothers will also receive either placebo or AZT.

Combination AZT and ddC in Stable AZT-Treated Pediatric Patients with HIV Infection (ACTG 190).—This is a multicenter, double-blind, randomized, outpatient study to evaluate the pharmacokinetics, safety and activity of ddC in combination with AZT in stable, AZT-treated pediatric patients between the ages of 3 months and 12 years. Patients will be randomly assigned to one of two treatment arms and stratified according to the duration of their ongoing AZT therapy.

Early Treatment with AZT in Asymptomatic Infants with HIV Infection (ACTG 180).—The purpose of this multicenter study is to determine the effect of early treatment with AZT in preventing the development of symptoms in HIV-infected infants. Infants less than 9 months of age will be randomly assigned to AZT or placebo, in a blinded fashion.

Non-Treatment Studies

Vertical Transmission.—Approximately 15% to 25% of infants born to HIV-infected mothers will be HIV-infected. It is currently not known which factors are responsible for protecting the majority of infants from infection. One potential explanation is the immune status of the mother. This laboratory-based study will evaluate the immune status of HIV-infected pregnant women and correlate these measurements with infection in the child. HIV-infected mothers may enroll in the study at any point during their pregnancy. Women are asked to donate several tubes of blood during each trimester and just before delivery, for laboratory measurement of immune function. Blood is also collected from the

placenta at the time of delivery. Infants born to mothers participating in this study are monitored at birth, at 8 weeks and at 6 months of age for evidence of HIV infection and immunity to HIV. Information gathered from this study will be used to direct vaccine and immune therapy for pregnant mothers in an attempt to prevent vertical transmission of HIV. Women may simultaneously participate in this study and the AZT-treatment study (ACTG 076) described above.

Observational Database (ODB) Project.—To understand the natural history of HIV infection, this study will collect data anonymously from large numbers of HIV-infected individuals. The Observational Database has enrolled more than 10,000 patients in the United States and Canada. Participants have data collected at each physician visit. The resultant database is being used to answer questions on the incidence of various opportunistic infections, the distribution of patients with certain characteristics, and response to various therapies.

HER Study.—The HIV Epidemiology Research Study (HER study) investigates the natural history of HIV infection in women. HIV-infected and non-infected women at high risk for acquiring HIV will undergo a comprehensive interview, physical and laboratory analysis on entry into the study and every 6 months. These data will be used to identify those features of HIV infection that are of greatest significance for women and to determine response to treatments used for HIV infection.

AIDS Immunology Study.—This laboratory study seeks to correlate *in vitro* measures of cellular immunity with

lack of progression of HIV disease or resistance to infection with HIV. Individuals will have measurements of cytotoxic T lymphocyte (CTL) activity and cell-mediated cytotoxicity (CMC) up to several times per year. Of particular interest are individuals who have: 1) been asymptomatic for more than 8 years; 2) been asymptomatic despite a low CD4 cell count; or 3) remained uninfected (HIV-) despite repeated high-risk activity or exposure.

How to Get More Information

Trials open for enrollment within BRUNAP are described in a periodically updated brochure. Newly open studies are announced in various newsletters and newspapers. A copy of the clinical trials brochure may be obtained by calling the BRUNAP office (863-1725). General information concerning clinical trials can be obtained by calling the Clinical Trials Office at 456-AIDS (456-2437). Alternatively, individuals interested in a particular trial may call the contact person listed with each trial.

For information on trials throughout the United States, call 1-800-TRIALS-A. For information of trials in Boston, call the Harvard AIDS Clinical Trials Unit at (617) 726-3815 or the Community Research Initiative of New England (CRINE) at (617) 424-1200.

Information on ongoing research in the field of HIV treatments can be obtained through national newsletters, such as BETA (Bulletin of Experimental Treatments for AIDS), AIDS Treatment News, Treatment Issues and the AmFAR AIDS/HIV Treatment Directory. The BRUNAP office (863-1725) has copies of these

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newsletters or can direct individuals as to where they can be obtained.

The Clinical Trials Process

Once you have obtained sufficient information on a clinical trial to determine whether you or your patients would be interested in participating, details of the inclusion and exclusion criteria should be discussed with the study nurse. At an initial screening visit, an interview is conducted by the study nurse to determine whether any exclusionary conditions are present. In addition, blood may be drawn to determine CD4+ cell count and whether serious laboratory abnormalities are present. In general, one or two additional visits are necessary before starting the study medication.

During the study period, medication is dispensed at clinic visits, which may be as frequent as weekly or as far apart as once every few months. At each visit, questions regarding side effects, concurrent illnesses, and medication compliance are asked. Periodically, a full physical examination is done. Additional studies, specific for each trial, may be included. Some studies offer compensation for travel, child care and other expenses, particularly if an admission to the hospital is required as part of the study.

Future Prospects

The BRUNAP Clinical Trials Program will continue to offer innovative, new therapies to HIV-infected persons in the Rhode Island area. Future studies sponsored by pharmaceutical companies, CBCTN and DATRI are anticipated. Vaccine studies, which will require the participation of potentially thousands of HIV-infected and non-HIV infected individuals, are anticipated to come to Rhode Island in the near future. Additional therapeutic studies may be offered through the Terry Bein Community Program for Clinical Research on AIDS (CPCRA); the closest CPCRA site is in New Haven, Connecticut. Our successful participation in clinical trials in the past several years promises to continue in the future, as we are able to offer an ever-widening array of treatment opportunities for our patients with HIV infection.

Acknowledgement

The author thanks Bill Jesdale of the Brown University AIDS Program for preparation of Figure 1 and gratefully acknowledges the principal investigators who contributed descriptions of their studies. We are all indebted to the participants in our studies,

who have joined us in the search for new and better therapies for HIV infection and disease.

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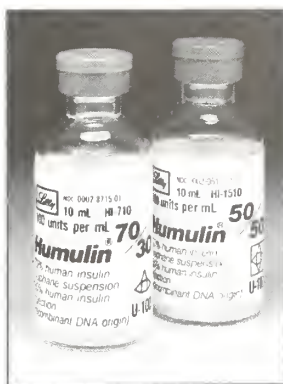
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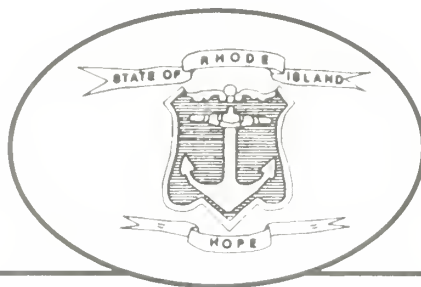


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HEALTH BY NUMBERS



Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Knowledge, Attitudes, and Beliefs Concerning AIDS and HIV

The Rhode Island Behavioral Risk Factor Survey (BRFS) was administered annually from 1990 to 1992 to about 1800 Rhode Island adults in households with telephones. The BRFS is a national random-digit-dial telephone survey sponsored by the Centers for Disease Control and Prevention, in 46 participating states to obtain information regarding chronic disease behavior. Recently, questions also have been asked regarding respondents' knowledge, attitudes and beliefs concerning AIDS and HIV.

Highlights for Rhode Island for the years 1990-1992 include:

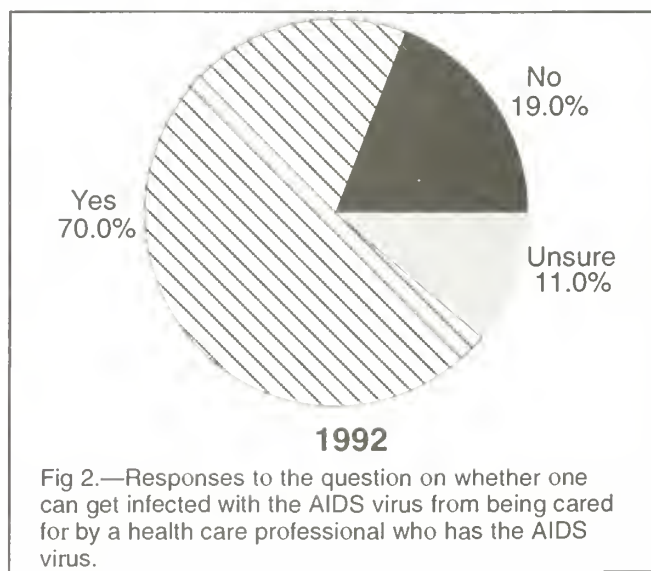
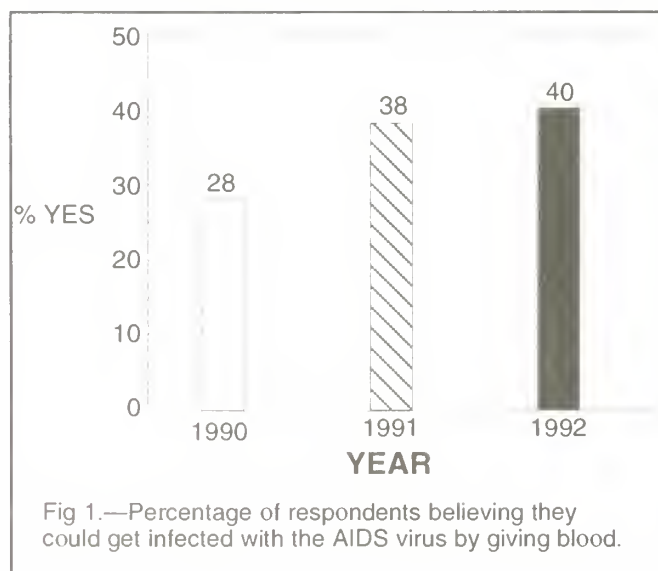
- The proportion of respondents who believed that a person could get infected with AIDS or the AIDS virus from giving blood increased from 28% in 1990, to 38% in 1991 and to 40% in 1992. Nationally, 39% of respondents are misinformed on this issue.
- Also of interest are the locations people believed they could go to for HIV testing: 35% thought hospital emergency rooms were a place for testing. Actually, only 30% of the hospital

emergency rooms surveyed in Rhode Island perform HIV testing; most make a referral to a clinic or testing site. Thirty-one percent of respondents thought they could receive HIV testing at a private doctor's office (those with higher socio-economic status more often indicated a private doctor's office as a place to go for HIV testing), which accurately indicates the location where the majority of HIV tests are conducted in Rhode Island.

- Six percent of respondents in 1991 and 1992 thought they could receive testing at the Department of Health. Also, 5% of respondents in 1991 and 4% in 1992 believed they could receive HIV testing at a blood bank. The Rhode Island Blood Center does perform anonymous testing for a charge, but blood donation to receive an HIV test is prohibited. Five percent of respondents in both years indicated they believed they could have their blood tested at a community health center; most health centers in Rhode Island

do provide HIV counseling and testing. Only 0.1% of respondents in 1991 and 0.3% in 1992 indicated that they believed they could have their blood tested for HIV at an STD clinic. (The RI Department of Health's STD Program processed 2095 HIV tests in 1990, 1907 tests in 1991, and 1669 tests in 1992). Eleven percent of respondents in 1991 and 13% in 1992 indicated they did not know where to go to get their blood tested or refused to answer the question. [N.B.: HIV testing with pre- and post-test counseling is available in Rhode Island at private physicians' offices, at the Rhode Island Department of Health's HIV and STD clinics at Whitmarsh House, at community health centers, and at the Rhode Island Blood Bank. Testing at the department's clinics is provided without charge; other sites may charge a fee. Emergency rooms are not recommended sites for testing because they are not ideal settings for pre- and post-test counseling.]

- In 1992, 70% of respondents indicated

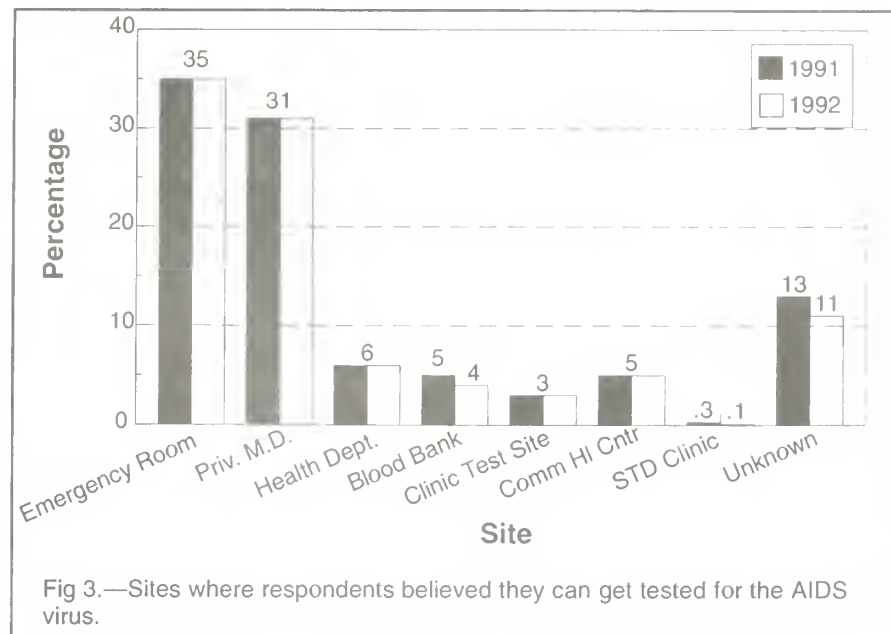


Submitted by Denise Bury Maynard, MPH, Office of AIDS/STD, RI Department of Health. Health by Numbers is edited by Jay S. Buechner, PhD, and William J. Waters, Jr., PhD.

that they believed they could get infected with the AIDS virus by "being cared for by a health professional who has the AIDS virus." Only 19% of respondents said that they could not get infected this way, and 11% were not sure or refused to answer.

The 1990-1992 BRFS data clearly indicates that Rhode Islanders need to be better educated regarding modes of HIV transmission. Based on their responses, some individuals seem to be taking unnecessary precautions, such as avoiding a restaurant where the cook was infected, shunning a day-care center where a child was infected, not wishing to work with an infected co-worker, or not giving blood for fear of contracting the HIV virus. The public needs to be encouraged to take necessary precautions to avoid HIV transmission, such as using a latex condom during sexual activity or abstaining from sexual activity, not sharing needles, and avoiding non-prescription intravenous drugs.

The data collected to date (via BRFS and other RI surveys focusing on HIV knowledge, attitude, behavior and beliefs) highlight particular problem areas concerning the community's knowledge level regarding HIV and AIDS. Various educational efforts are already under way



or are being developed through the RI Department of Health and contracting agencies in order to raise awareness of HIV issues and to combat some of the misconceptions regarding HIV and AIDS which the BRFS identified. These activities include: training of health professionals (including dentists and 3rd and 4th-year medical students), cultural sen-

sitivity training, RI Department of Health In-Service training (including training for staff serving people of color), Adult Correctional Institute Peer Education Program, health education and outreach to prostitutes, HIV education to incarcerated youth, and a public information campaign with special attention given to minority communities.

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VOLUME I
NUMBER 1

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

90 Years Ago (September 1903)

An editorial comments on the significant rise, each Fourth of July, of cases of tetanus "with alarmingly high mortality." Most of these patients are young boys who sustain wounds of their hands when they discharge their cartridge (ie, blank) pistols. The editorial points out "that the tetanus germ does not exist in the materials of the cartridge itself. The danger then would seem to be in the time of year and the condition of grimy hands under which the wounds are received." Appropriate treatment is then outlined. The editorial concludes with the following recommendation: "In view of the awful results reported this year it would seem that health boards, the medical profession, city officials and legislators, should promptly cooperate to do away with the present methods of celebrating the national anniversary, especially in the selling and use of the blank cartridge and the toy pistol, so called. The danger to boy life is too great to be disregarded and we believe our medical societies should take the initiative or lend their influence in this direction."

The lead communication is a lengthy treatise on the community and tuberculosis, written by Jay Perkins, MD, of Providence. The paper is best understood after reading Dr Perkins' prior article (in this Journal) on the need, in Rhode Island, for appropriate inpatient facilities for the exclusive care of those with demonstrable tuberculosis, the establishment of so-called sanitoriums. The current paper outlines the history of recent professional actions, resolutions and legislative acts in furthering the establishment of such institutions. In November 1902, \$5000 was granted to purchase land for a Sanitorium for Consumptives. In January 1903, \$75,000 was appropriated to construct the administrative building and two clinical wings. Thus, in the

words of the author, "there will, by another year, be opened up a new era for the tuberculous of this State." At the time that this paper was written, the author noted that there were but three places within the state where a consumptive might seek help. First was an isolated pavilion in Howard, among the state institutions. Admission to this pavilion, however, requires that the applicant be a transfer from one of the state's almshouses. Second, at St Joseph's Hospital, there are 34 beds devoted to the treatment of incurable consumptives. Third, there is a special out-patient department at Rhode Island Hospital, for the observation of consumptives, but no hospital beds are at the disposal of this clinic. How extensive is the problem of tuberculosis in Rhode Island? The author states, during the year 1902, there were 955 deaths from tuberculosis in Rhode Island, 851 from tuberculosis of the lungs and throat. The author comments, then, on the selective distribution of fatal tuberculosis in the state, affecting predominantly the lowest wage-earners, and the adverse effect, in general, of tuberculosis on the economic welfare of this community. In contrast, the successful experience of Germany in establishing a network of sanatoria is described, the author noting also the co-

incident reduction in mortality from tuberculosis in those jurisdictions with sanatoria. Dr Perkins then suggests that the private sector of the community take the initiative to help the medically helpless. He advises that a society for the care of consumptives be established to solicit funds for such care. The article ends with a chart showing comparative mortality rates for different diseases in Rhode Island. In 1901, about 1100 deaths were ascribed to tuberculosis, about 800 to pneumonia, 760 to heart disease, 560 to renal disease, 550 to stroke, 460 to infantile diarrheas, and about 390 to cancer.

50 Years Ago (September 1943)

Drs William J. Bell, MD, and Kalei K. Gregory, MD, assistant superintendents of Charles V. Chapin Hospital in Providence, are authors of the lead article describing massive arsenotherapy of early syphilis. The authors first provide the history of antiluetic therapies with massive doses of arsenical preparations from Ehrlich's earliest attempts. The procedure adopted by the authors requires intravenous injections (of 600cc volumes) each containing 60 mg of mapharsen delivered at the rate of 60 to 90 drops per

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minute. Thus during an interval of 5 days, each patient receives a total of 1200 mg of mapharsen. Toxic reactions included nausea and vomiting (69.1%), primary fever (88.3%), toxic dermatitis (5.9%), peripheral neuritis (10.3%), and hemorrhagic encephalitis (2.9%). The authors conclude: "A series of 61 patients was given massive mapharsen therapy for primary or secondary syphilis by the continuous intravenous drip method and 7 by the syringe method. There were no fatalities and only 2 cases of severe hemorrhagic encephalitis. The latter occurred in the group that received the continuous drip method. There was only one failure of treatment, which gives a rate of cure of 94.7% in the 18 cases followed for 1 year." They note, further: "Massive arsenotherapy of early syphilis is a relatively safe procedure if it is carried out in a hospital, if the cases are carefully selected, and if they are closely observed during treatment and for several days following treatment."

Clifton B. Leech, MD, describes the essentials of the diagnosis of heart disease. The author briefly touches upon the objective signs essential to the recognition of organic heart disease. These include: cardiac enlargement; persistent hypertension; marked, generalized arteriosclerosis; diastolic murmurs and palpable thrills; engorgement of neck veins and abnormal pulsations; gallop rhythm; serious disorders of cardiac mechanism; dilatation of the aorta; abnormal retromanubrial dullness; and coronary thrombosis and angina pectoris syndromes.

An article explains how a physician may estimate his income tax (in keeping with new federal laws concerning the filing of income tax estimates.) Other brief articles include a discussion on war-time graduate medical meetings, and news from the war fronts.

25 Years Ago (September 1968)

The lead article, by John Rock, MD, describes and comments upon the population explosion. After a detailed description of historic and contemporary methods of human birth control, the author concludes: "Although we have these various good methods of family limitation, the need and urgency of restriction are so great that other, even more generally acceptable methods, are required. Research into finer details of reproductive physiology and how harmlessly to harness it is urgently needed. There are tremendous resources for this in devel-

oped nations. If it is not pitifully wasted because of internal and international pride and belligerency, there will be plenty of money for us all to do our part in this war against social destruction. The United Nations is splendidly engaged in the grand effort to make all countries charitably considerate of the welfare of each other, for only in this way can any one of us achieve the peaceful strength that will enable all to approach the universal spiritual goal of humanity. The welfare of each depends on the welfare of all."

John W. Walsh, MD, describes menopause. He observes: "We find that due to increased longevity of the population, particularly of women, more and more women require treatment of menopausal and postmenopausal complaints and ills. The more common symptoms and phys-

iological as well as psychological changes are reviewed and discussed. Estrogen and androgen therapy has beneficial effects as well as limitations. The effects and dangers of long range progestogen therapy are not as well understood. We should therefore be more cautious in their utilization. We cannot promise our ladies that estrogens will restore them to everlasting youth — but we can assure them that they will be healthier, happier, more vigorous, and more contented members of our society."

Alex Burgess, MD, discusses the diagnosis of pulmonary tuberculosis with special reference to the leucocyte count.

Horace F. Martin, PhD, Herbert Fanger, MD, and John Pezzullo discuss the criteria for automating the hospital clinical pathology laboratory.



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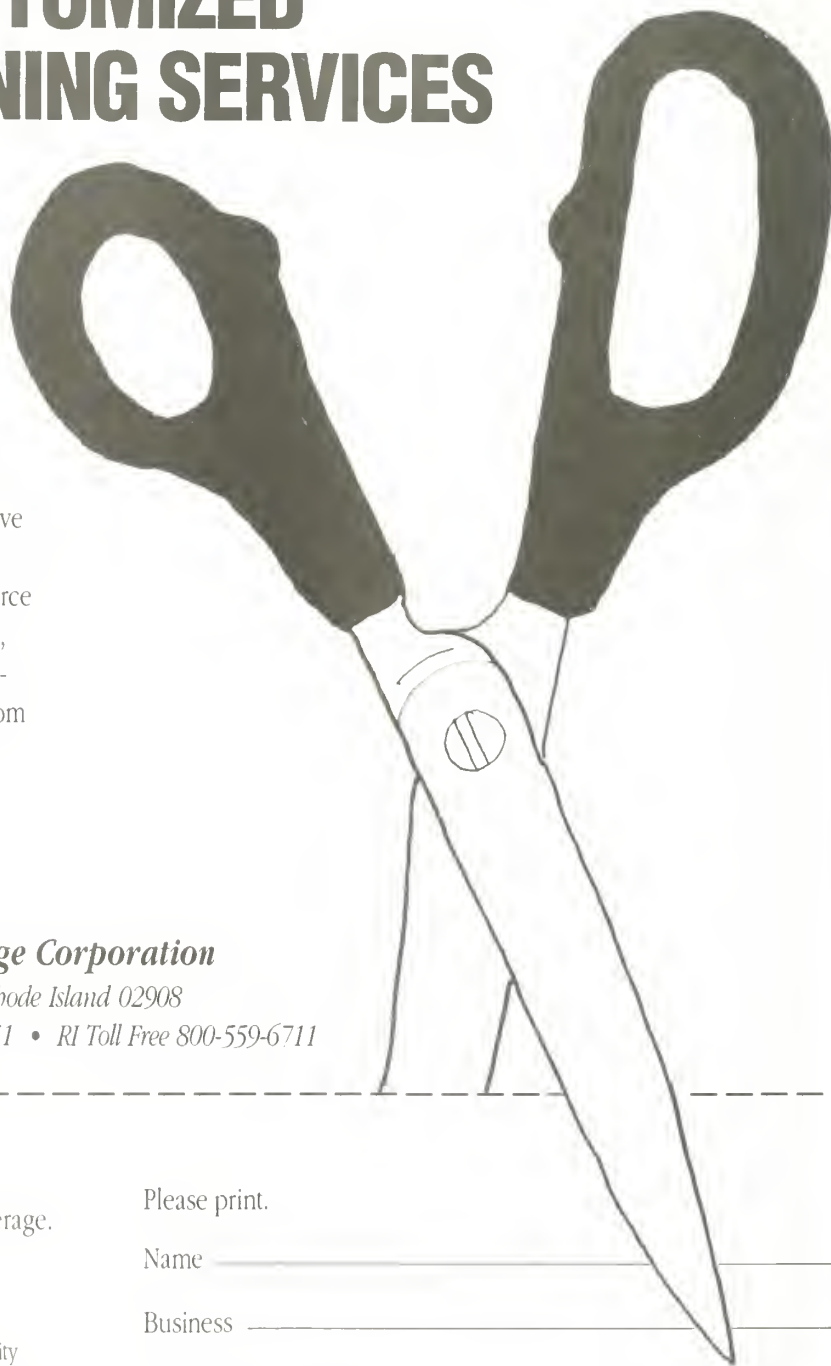
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Information for Contributors

Manuscripts - Manuscripts will be accepted for consideration with the understanding that they are original contributions, have never been published in its current form, and are submitted only to *Rhode Island Medicine*. An article should address a substantive issue of interest to the Rhode Island medical community. Articles may be no more than 3000 words in length and have no more than 20 references.

Specifications: Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins, using 8" x 11" non-erasable bond. Tables, charts, and legends should be submitted separately from the text and referred to by number (eg, Fig. 1 or Table 2, etc.) Number pages consecutively.

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Books:

2. Hollingworth JW. *Local and Systemic Complications of Rheumatoid Arthritis*. Philadelphia, Pa: Saunders; 1968.

Book Chapter

3. Epstein WL. Erythema nodosum. In: Samter M, ed. *Immunological Diseases*, 2nd ed. Boston, Mass.: Little, Brown; 1971;2:944-951.

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Reference: 1. Jones PH, et al. Once daily pravastatin in patients with primary hypercholesterolemia: a dose response study. *Clin Cardiol.* 1991;14:146-151

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis, hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin, the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SO 31.906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydrolysis metabolite (SO 31.945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, guanidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy).

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with placebo.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31.906 and SO 31.945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant increase in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SO 31.906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, anticoagulants (1 hour prior to PRAVACHOL (pravastatin sodium)), cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spiroinactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallenian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallenian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 2 year study in rats fed pravastatin at doses of 30, 100, or 300 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK + / - mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4 month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	4.4	6.9	2.0	1.9
Constipation	5.0	6.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo

The following effects have been reported with drugs in this class

Skeletal myopathy, rhabdomyolysis

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial palsy), tremor, vertigo, memory loss, peripheral neuropathy, peripheral nerve palsy

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthema, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting

Reproductive: gynecostasia, loss of libido, erectile dysfunction

Eye: progression of cataracts (lens opacities), ophthalmoplegia

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required

THE PRAVACHOL® DIRECTION
IN LIPID MANAGEMENT

Effective lipid management doesn't have to be tough



- Improves key lipids — significant reduction in LDL-C¹
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food


PRAVACHOL®
pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate. Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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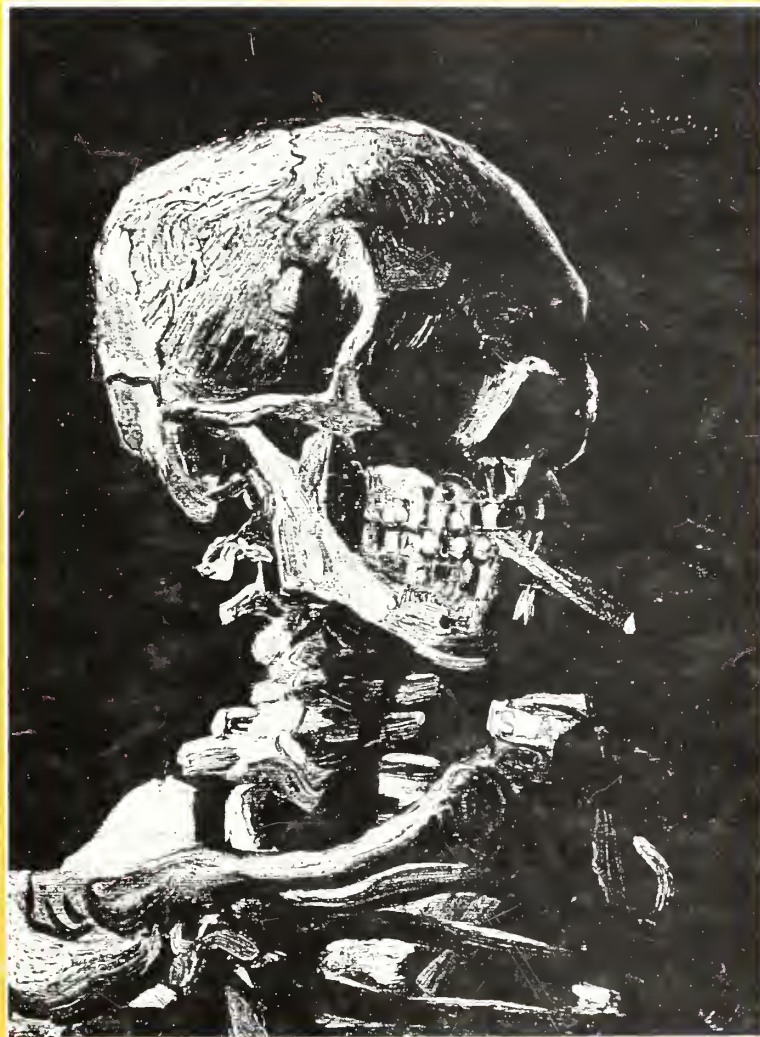
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Rhode Island **MEDICINE**

October 1993

Volume 76, Number 10

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Smoking in Rhode Island



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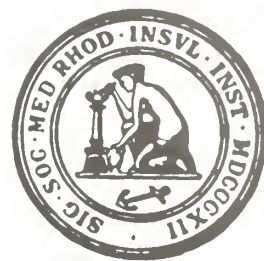
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Cover: Skull with a cigarette; oil on canvas by Vincent van Gogh, January 1886.

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Physicians Make a Difference

Smoking is a luxury we can ill afford. The annual excess illness cost of smoking in Rhode Island alone is estimated to exceed \$200 million. That's a lot of productivity down the drain.

Smoking is a complex problem, too big for any individual, group, or organization to tackle alone. Smoking is deeply rooted in our history, our culture, and our economy. It's tempting to youth and addictive to all.

Nonetheless, smoking is declining (from 45% of adults in 1955 to 25% of adults today), because more and more smokers are making the tough, individual decision that smoking is a luxury *they* can ill afford. Physicians have a unique role to play in this process. Patients look to their physicians as authorities on preventive health. If physicians do not promote smoking cessation firmly and consistently, can all those warnings on the cigarette packs be very important? Patients also look to their physicians for advice on how to quit and what to expect from different smoking cessation products like the nicotine patch.

As physicians, we can help our smoking patients in four ways, as suggested by the National Cancer Institute's manual for physicians, *How to Help Your Patients Stop Smoking*:

1. Ask about smoking at every opportunity.
2. Advise all smokers to stop.
3. Assist the patient in stopping (when they express their readiness to stop).
4. Arrange follow-up visits, reinforcing the decision to stop.¹

This approach is simple, direct, and takes little time. It recognizes that patients stop *when ready* and defines a realistic role for physicians in the process. We can't make our patients stop

smoking, as frustrating as this has been for all of us. We can guide them, however, and help them when they ask for it.

The article in this issue by Miller et al describes a comprehensive effort by the Rhode Island community to cut the prevalence of smoking in half by the year 2000. With your help, we can achieve this realistic goal.

Reference

1. National Cancer Institute. *How to Help Your Patients Stop Smoking*. Bethesda, Md: National Cancer Institute; 1989. NIH publication 90-3064. (For copies of this manual, call 301-496-5583.)

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A Loathsome Custom

The cigarette is the ideal addictive agent. It is universally available, relatively cheap, and socially sanctioned. It can be used at a moment's notice and in virtually any setting; it does not deprive the user of his faculties, and it requires no paraphernalia more complex than a match. In virtually every country, it may be legally assembled, distributed and sold with no hindrance other than taxation. The growing and curing of tobacco leaves are uncomplicated processes. Automated machinery can spew out billions of cigarettes, which are then neatly packaged to fit the pockets or pocket books of its users. The sequelae of cigarette usage are initially subtle, slow in appearing and are not intuitively linked to smoking. It is far easier, for example, to convince a court of law about causality with heroin than with cigarettes—despite the incontrovertible knowledge that millions of lives are compromised and abbreviated by the act of chronic smoking.

Until the current decade, smoking had been socially accepted, even actively encouraged. This encouragement was particularly evident in military life, and veterans of World War II will recall the free cigarettes included in every container of C rations. Cigarettes were said to increase social skills, keep idle hands busy, dispel anxiety, punctuate sex, and concentrate the mind on the task at hand. The realities, however, are otherwise. Cigarettes compromise breathing, accelerate atherosclerosis, increase the frequency of cancer, and at the very least, leave the mouth with a foul taste.

Great universities have been endowed with the profits of cigarette companies. And even tennis tournaments are named after certain brands. Moreover, until recently, cigarette packs could be readily purchased from vending machines in the lobbies of hospitals, centers of higher learning and halls of justice. The condemnations of smoking in current writings may even have served an unwanted purpose. "I have every sympathy," said Strauss, "with the American who was so horrified by what he had read of the effects of smoking that he gave up reading."

Only alcohol rivals cigarette smoking as the prime addictive burden of civilization. But while the effects of fermented grapes are readily noted in the Scriptures, addictive smoking comes into its own only in the late 16th century. Jean Nicot, the French ambassador to Portugal, introduced the tobacco plant to France in 1560 allegedly for its medicinal merits. About the same time, a number of Elizabethan adventurers (including Ralph Lane, John Hawkins, William Middleton and, of course, Walter Raleigh) brought the leaf back from the Virginia colony. Nicot's name has been perpetuated in the words *nicotiana* and *nicotine*; this dubious honor places him in a small class with others such as Charles Boycott, Dr Jo-

seph Guillotin and Jean Martinet whose names have been immortalized as uncaptialized, unsavory generic nouns. The word, tobacco, is derived, through Portuguese and Spanish, from an earlier Arawak (Caribbean) word.

Pipe-smoking of the dried and pulverized tobacco leaf became a stylish preoccupation in the early years of the 17th century. James I of England, (whose extramonarchial renown rests largely upon his sponsorship of a theologic committee assigned the task of translating the Bible into English), regarded smoking as an unmitigated vice. He wrote: "A custom loathesome to the eye, hateful to the Nose, harmful to the braine, dangerous to the lungs, and in the blacke stinking fume thereof, nearest resembling the horrible Stigian smoke of the pit that is bottomlesse."

Despite this royal condemnation, pipe-smoking flourished among both gentry and the working poor. The pipe was typically clay, inexpensive, and dispensable after a short interval of use. The smoker carried his tobacco box with him as well as a small pair of tongs to lift a glowing ember to light the tamped "divine weed." Tobacco was purchased from apothecaries or from tavern keepers. By the 18th century, shops arose that specialized in the sale of tobacco varieties (Virginian, Greek, Turkish) and smoking equipment. Numerous types of smoking tobacco now became available, often mixed with sundry spices (eg, anise) or which had previously been steeped in wines or brandies. And a writer, with great prescience, described the evils of smoking as, "very pernicious unto their bodies, too profluvius for many of their purses, and most pestiferous to the publicke State."

During the Great Plague of 1665, no London tobacconist was said to have contracted the bubonic disease. Similarly, tobacconists were seemingly immune to cholera during the epidemics of 1831, 1849 and 1866. Smoking then came to be regarded by many as a worthy bulwark against contagious airs and miasmas. As one elder stated: "It corrects the air by Fumigation and it avoids corrupt humours by Salivation." Whatever the mechanism, students in great public schools such as Eton were required to smoke pipes during the days of epidemic jeopardy.

In an age when illiteracy was the rule and houses went unnumbered, the various trades developed distinctive symbols so that they could be readily located. Tobacconists typically chose portraits of

Walter Raleigh, or a wooden statue of an American Indian (for the sale of Virginia tobacco). A picture of a Scots highlander usually denoted a store selling snuff.

Through the writings of inveterate smokers such as Tennyson much grace and gentility were imparted to an essentially dirty habit. Thackeray, for example, said that "the pipe draws wisdom from the lips of the philosopher, and shuts up the mouth of the foolsh; it generates a style of conversation, contemplative, thoughtful, benevolent and unaffected." And Mark Twain, rarely found silent on any contentious issue, stated: "I never smoke when asleep or when eating, never refraining at any other time."

Coffee houses, begun in the mid 17th century, opened new venues for tobacco

indulgence. A Spanish custom, the smoking of cigars or cheroots, took hold in England in the early 19th Century although pipe smoking, now some 200 years old, still predominated. The guild of pipe makers, incidentally, had been chartered in 1620. Clay pipes were now superseded by pipes carved from the dense wood of the heath tree (in French, this tree is called *bruyère*, hence, in English, briar.) Smoking clubs joined the coffee houses as sites for the gathering of those intent on smoking. The first of these clubs was the Marlborough on Pall Mall, London. Another was Carleton House. These names have been perpetuated as brand-titles of American cigarettes.

The original cigarette was probably a utilitarian response to left-over scraps of

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tobacco that were then crushed and enclosed in a piece of paper: in Spanish, called a *papalete*, a paper cigar for the very poor, particularly women. The first European cigarette factories were established in Spain, and the employees often women (one immortalized in Bizet's *Carmen*).

A number of wars and revolutions increased the social acceptance of these early paper cigars. During the later years of the French Revolution, smoking a proletarian device such as the cigarette was regarded as proof of one's belief in both *égalité* and *fraternité*. During the Crimean War, British and French veterans returned with an acquired fondness for tobacco leaf of Turkish or Russian origin. One of the earliest importers of these exotic eastern varieties of tobacco was a Mr Philip Morris of Bond Street, London. Many of the names of English brands, henceforth, bore Turkish or Russian names.

The major impetus toward addictive smoking, however, arose during the American Civil War. Northern troops became familiar with a variety of tobacco grown in the piedmont districts of Virginia and the Carolinas, called Carolina Bright. It was unique in that its nicotine content was six-fold greater than the Havana or Turkish varieties. Enlisted men found a pleasurable rush when they breathed in the smoke of this form of tobacco; inhaling became desirable rather than an event to be avoided. With no knowledge of alveolar exchange kinetics, these smokers nevertheless became the first to experience the authentic joys of smoking. Cigar and pipe smokers, on the other hand, rarely inhaled.

In the decade after 1875, cigarettes with a high nicotine concentration dominated the American market, to be blended shortly with another American variety called Kentucky Burley. This tobacco leaf provided yet another great virtue: it could readily absorb liquid additives such as sugar, rum, menthol or licorice to impart distinguishable "tastes" to each brand. A technological advance—Bonsack's invention of a practical and reliable cigarette-making machine—then opened the doors to the development of a major new industry.

By 1900, the sale of cigarettes exceeded all other tobacco products combined. Cigarettes were now socially acceptable and associated with youth, sophistication, weight reduction and athletic prowess. In contrast to cigars, where

appearance and aroma were paramount, the success of the cigarette depended upon its pharmacological effect.

Cigarette smoking, in the 20th century, evolved largely into a tale of advertising success and mass acceptance of what James I had called a loathsome custom. Historians, centuries hence, will look in

wonder at the credulity of nations in this era tolerating—indeed encouraging—the use of an unesthetic, disease-producing, addictive agent called the cigarette. As one person observed: there are no ifs, ands, or butts about it, cigarettes are deadly.

Stanley M. Aronson, MD

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Working in Harmony with How People Quit Smoking Naturally

James O. Prochaska, PhD

Behavior change is the goal that unites health promotion and disease prevention professionals. A factor that has retarded the field is our traditional reliance on a relatively unsophisticated concept of change. Most often we have defined change implicitly as the dramatic movement from chronic, unhealthy behavior to stable, healthier behavior. An example of such a shift involves smokers going from smoking 20 cigarettes a day for 20 years to none a day for the next 20 years.

What is wrong with this conceptualization besides the fact that it does not represent the way that most people change? It leads us to expect people to change quickly. So we offer short-term smoking cessation programs and are disappointed that 70% to 80% of the participants are still smoking a year later. People do not change chronic behaviors quickly. The best data available indicates that average self-changers take three to four serious quit attempts over 7 to 10 years before they successfully quit smoking. And we expect to be successful with one trial of intervention? We have been treating chronic behavior problems, like smoking, as if they are acute disorders.

When we began to study how smokers quit naturally without professional programs, we discovered that smokers progress through a series of five stages of change: precontemplation, contemplation, preparation, action and maintenance.

In precontemplation smokers are not seriously intending to quit in the next 6 months. Smokers in this stage are either unaware or under-aware of the long-term consequences of their smoking. Or, they may be demoralized about their abilities to quit and now they don't want to think, read, or talk about quitting. These smokers are resistant to quitting and are not ready for action interventions.

Smokers in the contemplation stage seriously intend to quit in the next 6

months but are not prepared to take action immediately. Contemplators are well aware of the benefits of quitting smoking but also over-evaluate the cons of quitting. Their ambivalence can keep them stuck in contemplation for years. "Some-day I'm going to quit smoking," they think. We often consider people stuck in this stage to be chronic contemplators—people who substitute thinking for acting or behavior change procrastinators.

Smokers in the preparation stage seriously intend to quit in the next month and typically have tried to quit in the past 12 months. They usually have a plan (ie, talking with their physician, going to a cessation program, obtaining a patch, or using a self-help program) and are prepared for action. They report some small behavioral changes, such as smoking five cigarettes less or delaying their first cigarette for 30 minutes longer than precontemplators or contemplators.

Action is the 6-month period following quitting. Initially we compared 0 to 3-month periods and 3 to 6-month periods and found no differences in the amount or type of strategies people use to continue to quit smoking. One problem is many smokers do not plan enough time for the action stage. They believe they can ease up on their efforts after only a few weeks or a couple of months. Such letting up puts them at much greater risk of relapse.

Individuals can let up more after 6 months of cessation, once they enter the maintenance stage. But, they can't let up entirely, or they are likely to relapse. Maintenance lasts from 6 months to up to 5 years. The field used to believe that the risks for relapse were pretty much over after 6 to 12 months of continuous abstinence. But, the 1990 Surgeon General's report shows that after 12 months of not smoking even a puff, 37% of maintainers eventually return to regular smoking. After 5 years of continuous abstinence from smoking, the risk of relapse drops to 7%, probably about as low as it will go.

Spiral Pattern of Change

Most people taking action to modify addictions do not successfully maintain

After 5 years of continuous abstinence from smoking, the risk of relapse drops to 7%, probably about as low as it will go.

their gains on their first attempt. With smoking, successful self-changers make an average of 3 to 4 action attempts before they become long-term maintainers. Because relapse is the rule rather than the exception with addictions, we found that we needed to modify our original stage model. Initially we conceptualized change as a linear progression through the stages; people were supposed to progress simply and discretely through each step. Linear progression is a possible but relatively rare phenomenon with addictive behaviors.

Figure 1 illustrates how most people move through the stages of change. In this pattern, people can progress from contemplation to preparation to action to maintenance, but most individuals will relapse. During relapse, individuals regress to an earlier stage. Some relapsers feel like failures—embarrassed, ashamed and guilty. These individuals become demoralized and resist thinking about behavior change. As a result, they return to the precontemplation stage and can remain there for various periods of time. About 15% of smokers who relapsed in our self-change research regressed back to the precontemplation stage.

Fortunately, this research indicates that the vast majority of relapsers—85% of smokers for example—recycle back to the contemplation or preparation stages. They begin to consider plans for their next action attempt while trying to learn from their recent efforts. The spiral model suggests that most relapsers do not revolve endlessly in circles and that they do not regress all the way back to where they began. Instead, each time relapsers recycle through the stages they potentially learn from their mistakes and can try something different the next time around.

Treatment Implications

Professionals frequently design ex-

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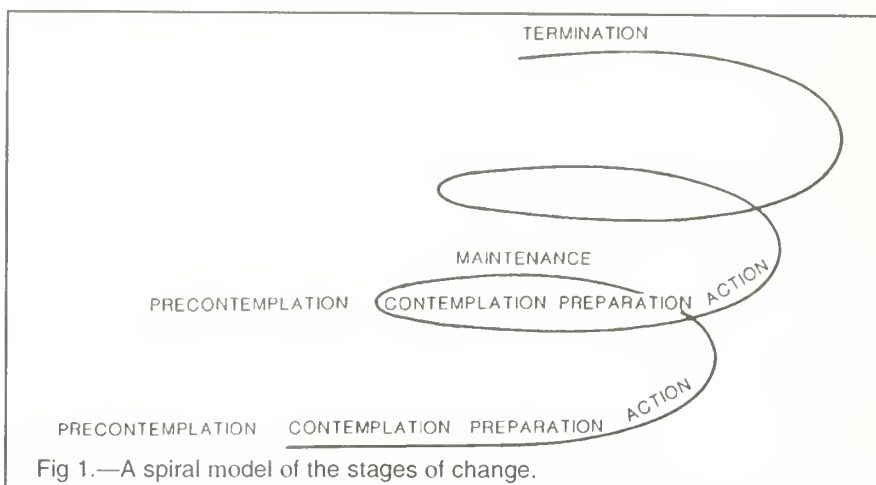
ABBREVIATIONS USED
CPRC: Cancer Prevention Research Consortium
HMO: Health maintenance organization

cellent action-oriented treatment and self-help programs, but then are disappointed when only a small percentage of addicted people register or when large numbers drop out of the program after registering. To illustrate, in a major health maintenance organization on the west coast, more than 70% of the eligible smokers said they would take advantage of a professionally developed self-help program if one was offered.¹ A sophisticated action-oriented program was developed and offered with great publicity. Only 4% of the smokers signed up. As another illustration, researchers compared four different recruitment strategies for home-based intervention programs for smoking cessation and weight control.² The recruitment rates ranged from 1% to 5% of those eligible for smoking cessation programs and from 3% to 12% for those eligible for weight control programs.

The vast majority of addicted people are *not* in the action stage. Aggregating across studies and populations 10% to 15% of smokers are prepared for action, 30% to 40% are in the contemplation stage, and 50% to 60% in the precontemplation stage.³ If these data hold for other populations and problems, then professionals approaching patients with only action-oriented programs are likely to underserve, misserve, or not serve the majority of their patient population.

Moving from recruitment rates to treatment outcomes, we have found that the amount of progress clients make following intervention tends to be a function of their pretreatment stage of change.³ Figure 2 presents the percentage of 570 smokers who were not smoking at four follow-ups over an 18-month period as a function of the stage of change prior to random assignment to four home-based self-help programs. Figure 2 indicates that the amount of success smokers reported after treatment was directly related to the stage they were in prior to treatment. To treat all of these smokers as if they were the same would be naive. Yet, that is what we traditionally have done in many of our treatment programs.

If clients progress from one stage to the next following an intervention, they can double their chances of taking action during the next 6 months.⁴ Of the precontemplators who were still in precontemplation at 1 month follow-up, only 3 took action by 6 months. For the precontemplators who progressed to contemplation at 1 month, 7% took action by 6 months. Similarly, of the contemplators who remained in contemplation at 1 month, only 20% took action by 6 months.



At 1 month, 41% of the contemplators who progressed to the preparation stage attempted to quit by 6 months. These data demonstrate that treatment programs designed to help people progress just one stage in a month can double the chances of participants taking action on their own in the near future.

Mismatching Stage & Treatment

A person's stage of change provides proscriptive as well as prescriptive information on treatments of choice. Action-oriented therapies may be quite effective with individuals who are in the preparation or action stages. These same programs may be ineffective or detrimental, however, with individuals in precontemplation or contemplation stages.

An intensive action- and maintenance-oriented smoking cessation program for cardiac patients was highly successful for those patients in action and ready for action. This same program failed, however, with smokers in the precontemplation and contemplation stages.⁵ Patients in this special care program received personal counseling in the hospital and monthly telephone counseling calls for 6 months following hospitalization. Of the patients who began the program in action or preparation stages, an impressive 94% were not smoking at 6-month follow-up. This percentage is significantly higher than the 66% nonsmoking rate of the patients in similar stages who received regular care for their smoking problem. The special care program had no significant effects, however, with patients in the precontemplation and contemplation stages. For patients in these stages, regular care did as well or better.

Independent of the treatment received, there were clear relationships between pretreatment stage and outcome. Twen-

ty-two percent of all precontemplators, 43% of the contemplators, and 76% of those in action or prepared for action at the start of the study were not smoking 6 months later.

A mismatched stage effect occurred with another smoking program. An HMO-based self-help smoking cessation program for pregnant women was successful with patients prepared for action but had negligible impact on those in the precontemplation stage.⁶ Of the women in the preparation stage who received a series of seven self-help booklets through the mail, 38% were not smoking at the end of pregnancy (which was approximately 6 months post-treatment). This was triple the 12% success rate obtained for those who received regular care of advice and fact sheets. For precontemplators, however, 6% of those receiving special care and 6% receiving regular care were not smoking at the end of pregnancy. These two studies portend the potential importance of matching treatments to the client's stage of change.

Matching Stage & Intervention

One of the most important findings to emerge from our self-change research is an integration between the stages of change and the processes of change smokers use to progress through the stages.⁷ In the early stages, smokers use cognitive, affective, and evaluative processes to change their thoughts, emotions and evaluations related to smoking. In progressing from preparation to action, they use existential and interpersonal processes to enhance their commitments to quit and the social support they can receive from others as they attempt to quit. During action and maintenance, they use more behavioral processes to modify the environments and their urges to smoke. These include controlling external cues to

smoke, countering thoughts and feelings that urge them to smoke, using substitutes for cigarettes such as nicotine gum or patches, and rewarding themselves for the successes they make over time or in highly tempting situations.

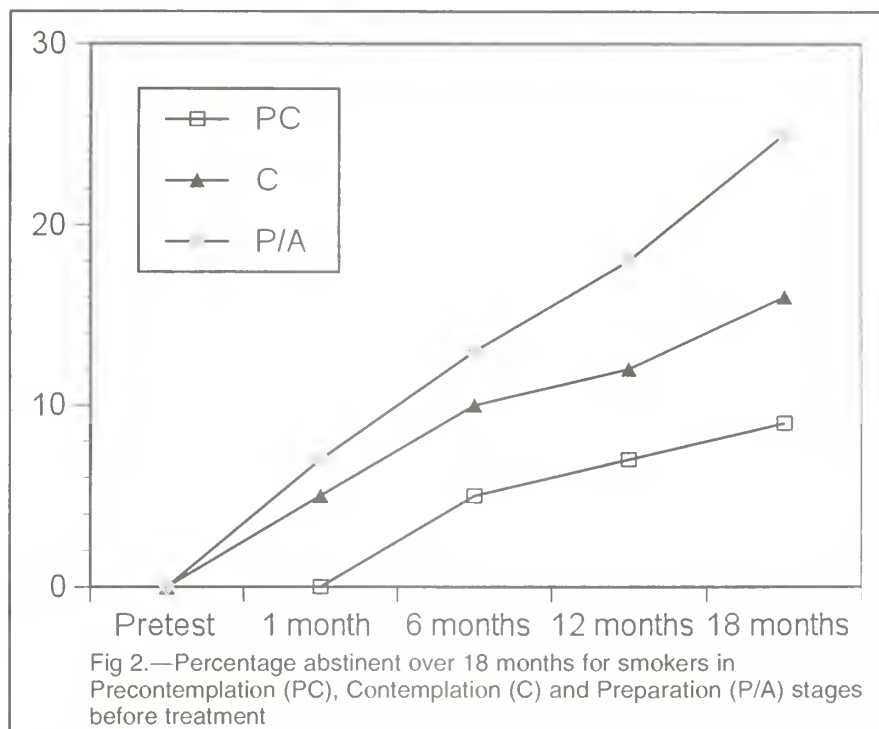
It is not only essential that individuals use particular change processes at particular stages. It is also essential that they use the processes frequently enough and for long enough durations. To maximize people's efforts to quit smoking, we have developed a computer-driven expert system that applies all the knowledge we have gained on how people quit naturally. This system helps smokers apply appropriate processes at particular stages at adequate dosages and durations. Over an 18-month follow-up period, this stage-matched program was found to be 2.5 times more effective than the best action-oriented program available. In two current clinical trials with 5000 smokers each, we are getting 60% to 75% participation rates compared to the 4% to 7% rates typically found with action programs.

This expert system is now available for commercial application in corporations through Johnson and Johnson's Health Maintenance Inc. We are working to make it available as quickly as possible for use in physician's offices and managed-care facilities.

Without this expert system, here are some tips on how physicians can help smokers progress from one stage to the next and thereby double their chances of not smoking in 6 months. Across 14 different health behavior problems, we have found that the pros of making a healthy behavior change must increase if individuals are to progress from precontemplation to contemplation. Therefore, with smokers, physicians can help them to become aware of the many advantages of quitting smoking. Most precontemplators can only name a couple of chronic diseases they can help prevent by quitting smoking. Physicians can teach them about the dozen diseases quitting smoking can help prevent.

By personalizing the greatest risks smoking presents for a particular patient because of their family history or because of current symptoms, physicians can facilitate affective and evaluative processes. But remember, the goal is to move them to contemplating quitting, not to get precontemplators to quit before they are prepared.

For the same 14 behavioral risk factors, the cons of making a healthy behavior change must decrease if individuals



are to progress from contemplation toward action. Cons of quitting include fears that the person will be more tense and stressed without smoking. Such fears can be countered by facts that ex-smokers are less stressed than continuing smokers within 6 months after they quit. If withdrawal symptoms of craving symptoms are major cons of quitting, then physicians are well positioned to prescribe nicotine replacement treatments that counter such cravings. Of course physicians should advise patients against relying too heavily on nicotine replacement techniques at the expense of a well-planned behavior change program.

For patients who are prepared to take action, then physicians can progress full speed ahead with the best action-oriented interventions available. One of the attractions of the stage model is that professionals continue to apply the best interventions they have learned for helping patients take action to quit smoking. One of the differences is they try to match these action interventions to patients who are best prepared to benefit from them. With the expert system we have developed and with tips for smokers in earlier stages, we can become much more ambitious in our goal to help all smokers at risk and not just the 20% or less who are prepared to take action.

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Identifying and Assisting Smokers Who Have Difficulty Quitting on Their Own

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In a recent review, Lichtenstein and Glasgow¹ refer to smoking as a "vexing and fascinating problem" because of the relatively low quit rates for even the most intensive smoking cessation programs. Although there has been a steady decline in the prevalence of cigarette smoking since the late 1960s, smoking continues to represent the most preventable contributor to premature death, major disability, and unnecessary expense in the US.² Recent public health research has found that the majority of persons who quit smoking do so on their own or with the aid of low-cost self-help or public health interventions.³ However, many smokers are unable to quit on their own. Relapse to smoking remains a consistent problem, and most cessation programs can only claim abstinence rates of 20% to 30% after 1 year.⁴ These rates are a testimony to the strength of smoking's social, psychological, and biological fac-

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tors. Although not always recognized as such, nicotine has been demonstrated to be an addicting and dependence-producing drug.⁵ For this reason, there is a growing consensus that for treatment to be successful, an integrated, biopsychosocial approach is necessary.^{5,6}

Research has begun to focus on identifying the characteristics of smokers who are unlikely to remain abstinent, and there appear to be subpopulations of smokers who have particularly low quit rates or who are prone to relapse. Their special needs are often overlooked by typical smoking cessation interventions, thus making cessation improbable for these smokers. The role of the physician in intervening with these smokers is critical. We will suggest an approach based upon theoretical models of behavior change to help guide appropriate interventions to smokers who have difficulty quitting on their own. This paper will highlight specific groups of smokers who may require specialized interventions to increase cessation rates. Suggestions for identification, assessment, and treatment of these groups will also be presented.

A Game Plan: Preparing to Intervene

A recent shift from clinical to public health research has allowed for evaluation of new theories and provided important knowledge about the "natural evolution" of smoking behavior (see Prochaska this issue). In smoking cessation, successfully quitting was found to be a process that often requires a series of attempts over several years. Quitting smoking is now viewed as a process of identifiable stages that a person goes through in making this behavior change.⁷ The process occurs gradually over time, and explains why people respond differently to various cessation programs. Clearly, not all smokers are ready to quit on their own or with provider assistance. As few as 10% of all smokers may be ready to try to

... nicotine has been demonstrated to be an addicting and dependence-producing drug. For this reason, there is a growing consensus that for treatment to be successful, an integrated, biopsychosocial approach is necessary.

quit smoking.⁸ For this reason, assessing a person's readiness to quit smoking, and then matching an intervention to their stage of readiness for change is essential.

Treatment providers often are frustrated by patients' seeming lack of commitment to stop smoking. In theoretical models of behavior change, "commitment" can be recognized within the constructs of self-efficacy and perceived vulnerability. Self-efficacy is the belief that one is able to perform a recommended behavior change, while perceived vulnerability is the belief that one is susceptible to health problems. In smoking cessation, high levels of self-efficacy and perceived vulnerability are powerful predictors of successful quitting. Those patients with low self-efficacy or low perceived vulnerability are not likely to be ready to quit. Persons in the early stages of readiness may be better served by interventions that do not have cessation as the immediate goal. Instead, strategies to personalize the health risks of smoking and enhance self-efficacy will help to enhance the person's motivation to quit. For example, providing persons with feedback from lung function tests could allow them to reach their own conclusions about the negative consequences of smoking and move closer to quitting. Similarly, informing patients about their cigarette brand's nicotine level could prompt a change to a lower nicotine brand in preparation to quit.

Planning interventions according to a patient's level of readiness is more likely to influence variables of self-efficacy and perceived vulnerability, and therefore can better address the complex issues regarding smoking cessation and continued abstinence. Subgroups of smokers may need special considerations

ABBREVIATIONS USED:

AA: Alcoholics Anonymous
CAGE: Cut, Annoyed, Guilty, Eye-opener
ETS: Environmental tobacco smoke

for successful cessation. These groups are likely to have concurrent physical or psychological problems and, therefore, have increased contact with medical and mental health professionals. They are likely to have had difficulties quitting in the past and often present as not prepared to quit smoking. Being able to identify these smokers and having a strategy for smoking cessation is an important part of total patient care.

Smokers Likely to Benefit from Specific Interventions

High Nicotine Dependence

Highly nicotine-dependent smokers have greater difficulty in quitting.⁹ Factors indicating high nicotine dependence are: high smoking rate (ie, more than 25 cigarettes per day), high nicotine level of cigarette brand, inability to abstain when ill, and smoking soon after awakening.¹⁰ Smoking within 30 minutes of awakening may be the most powerful predictor of cessation outcome and can be used alone as a guide for determining if a patient is highly nicotine dependent.¹¹ Nicotine dependence can be assessed easily and reliably by the eight items of the Fagerstrom Tolerance Questionnaire.¹⁰ Smokers who are highly nicotine-dependent are most likely to experience withdrawal symptoms upon quitting, and the discomfort of withdrawal symptoms frequently leads patients to terminate quit attempts. Therefore, self-directed quit attempts or psychological approaches may be insufficient to help these smokers remain abstinent and are most likely to benefit from nicotine replacement strategies.

The most common nicotine replacements, nicotine gum and nicotine transdermal patches, are now readily available by prescription. The transdermal patches deliver a steady and more consistent dose of nicotine when compared to nicotine gum and appear to increase patient adherence. Transdermal patches are being produced by several companies and vary slightly in recommended prescription. Most are designed to be taken in a three-part course, with a higher dose patch (21 mg delivered per 24 hours) worn initially followed by reduced dosages (14 mg, 7 mg) over the course of 8 to 12 weeks. Patients smoking more than a pack per day of a high nicotine content cigarette will be getting less nicotine when placed on the 21 mg patch so that even with the patch some withdrawal symptoms are possible initially. However, these should subside relatively quick-

ly as the patient's body adjusts to the new level of nicotine. Early studies with transdermal patches have demonstrated their effectiveness for short-term abstinence.⁶

For highly nicotine-dependent smokers who are not candidates for the patch (eg, pregnant smokers, those who cannot tolerate the side effects, or those who cannot afford this treatment), a procedure called nicotine fading can be used to reduce daily nicotine intake.¹² Smokers work towards a target quit date by switching brands to progressively lower nicotine content cigarettes over several weeks. A rough estimate of a patient's daily nicotine intake can be computed by multiplying the average number of cigarettes smoked per day by the nicotine yield per cigarette. Lists of the nicotine content of the majority of US-made cigarettes can be given to patients to help them choose brands, and are readily available.^{13,14} Using nicotine fading, withdrawal symptoms tend to be experienced more diffusely over time and less intensely at quit date when total abstinence is attempted.

It is important to realize that nicotine replacement strategies used alone, without adjunct treatment, are not considered to be effective treatment for promoting long-term abstinence. Identifying and treating the highly nicotine-dependent smoker using nicotine replacement in combination with counseling or other forms of behavioral treatment, hold promise for heavily dependent smokers previously discouraged by failed quit attempts.

Depression

Although it has long been suspected that smoking relapse is triggered by negative affect,¹⁵ recent studies are just now beginning to confirm that self-reported depression and smoking prevalence are strongly associated. For example, among the general population of adults in the US, smokers with major depressive disorder¹⁶ or depressive symptoms¹⁷ are less likely to quit smoking than nondepressed smokers. Additionally, smokers report higher levels of depression than nonsmokers.¹⁸ In smoking cessation studies, patients with a lifetime history of major depression had significantly poorer long- and short-term abstinence rates after treatment than did patients without a history of depression, independent of the effects of gender or treatment.^{19,20}

For the physician, assessing a patient's depressive history before quitting may be useful when planning treatment. Nicotine may function as a mood regulator for those patients with a history of depression. These smokers may be par-

ticularly vulnerable to feelings of deprivation when attempting to quit and may benefit from specialized adjunctive treatment. Preliminary evidence indicates that pre-treatment with antidepressants may prevent the development of abstinence-related depressive symptoms with this group of smokers.²¹ Other treatment implications have only recently been addressed. If a patient is concurrently seeing a therapist, it may be necessary to coordinate decisions about the timing and mode of their quit attempts. Patients taking antidepressants for an affective disorder may need to have prescription adjustments made during and after quitting due to possible increases in depressive symptoms. Patients and their therapists can be educated about nicotine withdrawal, thereby reducing the confusion of these symptoms with exacerbation of a primary depressive disorder. Patients with a history of depression may benefit from increased support during a quit attempt. Referral to an individual therapist or specialized treatment that can address coping skills, self-efficacy, and techniques to manage negative mood while quitting smoking may be warranted. These special efforts may help increase quit attempts and long-term cessation rates for this group of smokers.

Other Psychiatric Comorbidity

Health professionals are also beginning to recognize the special challenges presented by smokers with psychiatric comorbidity. For example, Hughes et al²² concluded that 50% to 84% of psychiatric inpatients smoke, compared to 27% to 58% of nonpsychiatric inpatients. Smoking rates were also found to be elevated among psychiatric outpatients with diagnoses of schizophrenia (88%), mania (70%), anxiety disorder (47%), major depression (49%) and personality disorder (46%). Smoking may have a special hold on psychiatric populations because of nicotine's effect on neurotransmitters,²² thus making it more difficult for this population to quit. Beyond the known health risks, smoking has potentially negative psychiatric consequences. For example, smoking reduces the blood levels of many psychoactive drugs and worsens neuroleptic side effects.^{23,24} Unfortunately, psychiatric patients are rarely advised to quit smoking by either health or mental health professionals,²⁵ possibly because of assumptions that they will fail, they are not interested or that smoking cessation will complicate their psychiatric picture. Indeed, nicotine withdrawal symptoms such as restlessness,

anxiety, and inability to concentrate can mimic those of several psychiatric disorders²⁶ and may derail attempts to quit.

These findings raise questions about the need for specialized interventions for smokers with psychiatric comorbidity.²⁷ Patients with known or suspected psychiatric disorders should be questioned about the nature and history of their illness. Decisions about the timing and mode of their quit attempt should be made in conjunction with their mental health providers, based upon the severity and course of their disorder. Patients and their therapists should be educated about nicotine withdrawal so that symptoms will not be mistaken for psychiatric relapse. Patients should also be instructed to alert their mental health providers about the need to monitor, and possibly alter, their dosages of psychotropic medications during quit attempts. If it can be arranged, extra contact with their therapists may also help during the critical early stages of smoking cessation. Smokers with psychiatric comorbidity should not be automatically dismissed as hopeless cases. With the proper support, they may be able to quit.

Alcohol and Substance Abuse

Problem drinking and drug use can complicate any medical treatment. Studies show that up to 90% of heavy drinkers also smoke.²⁸ Drinking alcohol and smoking is associated with increased cancer risks.²⁹ Being in social situations where alcohol is consumed is a leading "high risk situation" for relapse to smoking in those who are trying to quit.³⁰ The commonalties, differences, and interactions among tobacco and other substances are gaining strong research attention.

Alcohol and substance use can be viewed on a continuum from occasional, socially acceptable levels of use to problematic, abusive, and dependence-producing use. When assessing and treating all persons interested in smoking cessation, it is important to know that their drinking and drug use are not problematic. Patients may not be aware of the strong relation between smoking and alcohol consumption. All patients identified as drinkers should be advised to monitor their alcohol consumption closely during quit attempts. The CAGE questionnaire³¹ is a useful screening device to identify problem drinkers by asking four questions:

Have you ever felt you should CUT down on your drinking?

Have people ANNOYED you by criticism of your drinking?

Have you ever felt GUILTY about your drinking?

Have you ever had a drink first thing in the morning (an EYE-OPENER) to steady your nerves or get rid of a hang-over?

Patients who answer "yes" to any of these questions are considered at risk for alcoholism, and further assessment may be needed to determine if formal treatment is necessary. A "red flag" for problem drinking or drug use could be manifested in a patient's resistance or defensiveness toward suggestions to abstain or reduce intake during quit attempts.

Persons in recovery from alcohol or drug abuse problems have traditionally not focused on smoking cessation.³² It is possible that smoking rates in these populations remain high due to the lack of an emphasis on nicotine as a drug of abuse in formal treatment programs. This issue does appear to be gaining some attention; chemical dependency programs are beginning to incorporate smoking cessation as a part of treatment and some AA meetings are now designated as non-smoking meetings. Researchers and treatment programs for alcohol and drug addictions are now simultaneously treating nicotine dependence or incorporating smoking cessation as a routine part of outpatient follow-up treatment. The fears that smoking cessation will jeopardize sobriety in recovering addicts have not been realized so far.³³

Implications for smoking cessation treatment providers include identifying problem drinkers or drug users and counseling them to consider addressing these problems before quitting smoking. All patients will need to be made aware of the association between alcohol, smoking, and risk for relapse. For the patient in recovery from drug or alcohol abuse, it would be important to describe expected withdrawal symptoms associated with quitting smoking and dispel irrational beliefs about quitting. Additionally, supportive therapy may be needed so that the patient does not jeopardize sobriety. Treatment providers can capitalize on the motivation of a person already making lifestyle changes in one area by providing smoking cessation counseling that complements these efforts.

Hospitalized Smokers and Smokers with End-Stage Disease

The Joint Commission for Accreditation of Health Care Organizations³⁴ has recently mandated that all hospitals become smoke-free institutions. This requirement has challenged health care

providers to develop policies to facilitate smoking cessation in patients while they are in the hospital. In many cases these patients are in the early stages of readiness to quit, and they resent having to stop smoking during hospitalization. Providing these patients with nicotine replacement strategies to manage withdrawal symptoms can increase adherence to hospital policies, especially for those not ready to quit. Other patients may be ready to receive information and treatments aimed at longer-term cessation. For example, one study found that 61% of post-MI patients randomly assigned to receive a nurse-managed, brief behavioral intervention for smoking cessation were abstinent at 1-year follow-up as compared to 32% of those receiving standard care.³⁵ Helping hospitalized patients to comply with smoking bans may also increase their self-efficacy about their ability to quit, and enhance their motivation for future cessation.

Patients with end-stage disease regularly see their physicians and are frequently in the hospital. Interestingly, the patient with end-stage disease is often excluded from smoking cessation interventions.³⁶ Eliminating this group from smoking interventions tacitly implies that patients with terminal illness may benefit more from continued smoking than from quitting. However, patients with end-stage disease can enjoy many of the same immediate rewards from quitting smoking that other smokers can. These include increased oxygenation to all body systems, improved circulation, increased activity tolerance, and reduced risk of respiratory infections.³⁷ These benefits can have a major impact on survival and quality of life, in that patients often succumb to complications of their disease, rather than the disease itself. In oncology patients, for example, the pulmonary system is often the first organ to fail, regardless of underlying pathology.³⁸ Therefore, quitting smoking can help minimize respiratory demise and related life-threatening sequelae in this population. Furthermore, a study evaluating the construct "hope" among patients with cancer and other chronic illnesses showed that 91% had set goals for themselves, many of which were to be achieved within 1 to 5 years.³⁹ A goal of quitting smoking is attainable. Quitting may afford patients a sense of self-fulfillment and personal control undermined by the disease process.

As with other smokers, it is crucial to determine the patient's readiness and interest in quitting. Smokers with end-

stage disease may believe they have nothing to gain from quitting, and therefore, will likely be in the early stages of readiness for change. These patients may need information on the health and psychological benefits of quitting to help them evaluate the pros and cons of attempting to quit. It is important to offer support and assistance to the patient while emphasizing that the patient has ultimate control over this decision.

Pregnant Smokers

Smoking during pregnancy subjects both the mother and the unborn child to considerable risks. Maternal smoking is associated with increased spontaneous abortions, complications during the pregnancy, premature and low birthweight babies, and other genetically related problems for the infant.^{2,40} The health risk for the unborn child returns to normal if the mother stops smoking in the first trimester, and quitting late in the pregnancy also reduces the risk of complications at birth. Parental smoking postnatally exposes the newborn to environmental tobacco smoke (ETS) at a critical time of lung development and contributes to higher rates of respiratory disease. Studies have demonstrated dose-related deleterious effects of ETS on pneumonia and other respiratory illnesses in children of smokers.⁴¹ Given the increased health risks and the strong attention to this issue by the medical community, it is not surprising that more smokers make quit attempts when pregnant. Current estimates indicate that 20% to 40% of pregnant women attempt to quit during pregnancy.⁴² Most patients, however, only cut down, and as many as 70% relapse during the pregnancy or within 6 months after delivery.⁴³ Many women plan only to quit during the pregnancy, returning to their previous level of smoking after the birth.

Researchers have started to address this issue only recently. While little is known about the processes and strategies that are the most effective for this special population, assessment of maternal smoking and counseling should occur during visits for routine prenatal care. Medical professionals, however, also need to educate pregnant smokers and their partners about the health risks of ETS exposure for their children. Smoking cessation programs designed for both pregnant women and their partners would appear particularly appealing. Nicotine replacement strategies are not recommended during pregnancy, therefore nic-

otine fading may be the best approach for patients with high nicotine dependence. Behavioral treatments including training spouses in positive and supportive behaviors may enhance coping during pregnancy and increase quit rates. Providing specialized cessation treatments during pregnancy increases cessation rates⁴⁴ and can have far reaching health benefits for these women and their families.

Minorities and Lower Income Smokers

In a recent report of the Surgeon General,² the prevalence of smoking was highest among individuals who were less educated and of lower-socioeconomic status. Of special concern is the overrepresentation of minority and ethnic groups within this population. This is particularly alarming because smoking exacerbates a number of serious illnesses that disproportionately affect minorities including hypertension, diabetes, low birth weight, and infant mortality.⁴⁵ African-Americans and Hispanics suffer the nation's highest rates of morbidity and mortality from smoking-related disease. It has been found that African-American smokers are more likely to have attempted to quit than white smokers, but are also less likely to attain long-term abstinence.⁴⁶ Cultural insensitivity, literacy and language barriers, and lack of basic health care services may alienate or exclude these smokers from standard smoking cessation programs. African-American smokers report physician advice to stop smoking less frequently than the general population, although minority smokers may be more willing to follow such advice.⁴⁶ Several large-scale evaluations of smoking and quitting patterns of African-American and other ethnic and racial groups are on-going.⁴⁷ Efforts to target culturally sensitive materials to appropriate literacy skills are underway. What may be needed, however, are innovative, low-cost strategies to reach these populations.

Physicians working with minority, lower income, or less educated populations can be powerful sources of smoking cessation assistance. Clarifying misconceptions about cancer risks and personalizing health related problems of smoking could help patients in their decision to quit. Treatment costs may represent a significant barrier for this group of smokers; voluntary health organizations, such as the American Cancer Society⁴⁸ or the American Lung Association,¹⁴ provide a reputable lower-cost

treatment alternative. These organizations also provide free self-help materials to treatment providers, and these can be distributed from clinics and offices to help promote smoking cessation. Many communities also have medical centers and universities with no- or low-cost research treatment programs.

Conclusion

Physicians will have varying levels of contact with smokers that appear to need special consideration concerning smoking cessation, and intervention strategies can be tailored to this level of interaction. It appears that these groups are underserved by treatment providers for different reasons. Providers of treatment to patients with psychiatric conditions or substance abuse problems may not address smoking cessation because of fears that this will interfere with other treatment plans or that it will overwhelm the patient. Physicians treating patients with end-stage disease may assume that this is not a worthwhile issue to pursue. Conversely, it may be assumed that all pregnant smokers will quit, underestimating the difficulty of quitting at a time when so many other changes are occurring due to pregnancy. Smoking cessation interventions have often been inaccessible to those with lower levels of education and socioeconomic status because of financial cost or inconvenient location. For example, the nicotine patch represents a potentially efficacious treatment, but may not be a viable option for lower income smokers at current cost. Finally, physicians and other health care providers may believe that helping a patient to quit is too much work, particularly if a patient does not "volunteer" to quit.

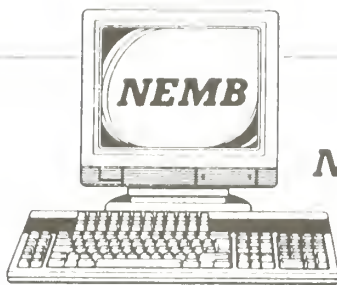
It is our view that the health risks associated with smoking for the smoker and the passive recipient of ETS warrant efforts to intervene for any group. The populations of smokers described may come to represent the "norm" for smokers of the future. Less nicotine-dependent smokers and those with fewer complications are more likely to quit on their own or with minimal intervention. The groups of patients described have psychiatric or complicated medical conditions and will utilize hospitals and health clinics more frequently than the general population. This places physicians, psychiatrists, psychologists, nurses, and drug rehabilitation counselors in a unique position to offer a variety of interventions. By recognizing and appreciating the characteristics of specific groups of smokers,

and by tailoring interventions to their particular needs, we can improve their quality of life by reducing a major health risk.

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Tobacco Use Control in Rhode Island: The Project ASSIST Blueprint for the 1990s

Judith R. Miller, MPH, John P. Fulton, PhD, Arvin S. Glicksman, MD,
David A. Chatel, MA, Margaret E. Kane, BS, Steven E. Slaughter, BA

Rhode Island is well on the way to becoming a smoke-free society.

Twenty-nine years after the publication of the Surgeon General's landmark report on the health hazards of smoking, Rhode Island is still beset by tobacco use and its sequelae. Twenty-three percent of Rhode Islanders smoke, including more than 25% of high school seniors. Tobacco use accounts for about 15% of all deaths in the state (roughly 1500 each year). A third of residential fire deaths are smoking related. The per capita cost of illness and death from tobacco use in Rhode Island is the highest in the country: \$284 per person (a staggering \$284 million annually).

These problems have not been ignored. Many organizations have worked persistently to reduce the prevalence of tobacco use in the state. Foremost is the Coalition on Smoking OR Health, which includes the Rhode Island Lung Association, the Rhode Island Division of the American Cancer Society, and the Rhode

Island Affiliate of the American Heart Association. The RI Department of Health and the Cancer Control Research Consortium, including the University of Rhode Island, the Miriam Hospital, and Brown University, have also played important roles, as have the RI General Assembly, many employers, and local drug abuse prevention task forces.

Through the work of these organizations, public exposure to environmental tobacco smoke in public buildings and public conveyances has been limited and

access to tobacco among youth has been restricted. The media have promoted new policies and kept anti-smoking messages before the public. Smoking prevention modules have been incorporated in school health curricula. A solid infrastructure of alternative smoking cessation programs has been built throughout the state. Rhode Island's tobacco use is monitored regularly with telephone surveys sponsored by the Centers for Disease Control and the National Cancer Institute. Finally, basic research has been conducted on

ABBREVIATIONS USED

ACS: American Cancer Society
EPA: Environmental Protection Agency
ETS: Environmental tobacco smoke
NCI: National Cancer Institute
PTA: Parent Teachers Association

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Table 1.—Draft objectives & strategies for the community environment channel

Objective 1

By 1998, cues and messages supporting non-smoking will have increased and pro-smoking cues and messages will have decreased in communities throughout Rhode Island.

Strategies:

- 1.1 Promote public actions supporting smoke-free environments.
- 1.2 Encourage media support for adoption of mandatory and voluntary smoke-free policies.
- 1.3 Increase the anti-smoking messages on radio, particularly messages that are targeted to ethnic and non-English speaking populations.
- 1.4 Increase the use of network and local cable TV for non-smoking messages.
- 1.5 Petition regulatory authorities to restrict or ban tobacco advertising within the scope of their authority.
- 1.6 Promote understanding of the EPA's designation of Environmental Tobacco Smoke as a cancer causing agent for humans.
- 1.7 Avoid tobacco advertising on government property.
- 1.8 Persuade sponsors of community events to reject cigarette advertising and tobacco promotion during the events.

Objective 2

By 1998, increase public support to enforce and enhance policies that mandate clean indoor air, restrict access to tobacco by minors, and increase economic incentives to discourage use of tobacco products and restrict advertising and promotion of tobacco.

Strategies:

- 2.1 Strengthen public awareness of tobacco as an addictive drug that requires appropriate public policy response.
- 2.2 Strengthen public awareness that environmental tobacco smoke is a human cancer causing agent.
- 2.3 Develop and implement meaningful enforcement of the Rhode Island Clean Indoor Air Act.
- 2.4 Increase the number of restaurants that are smoke free, especially those that cater to children and their families.
- 2.5 Prohibit youth access to tobacco from vending machines by limiting cigarette vending machines only to bars.
- 2.6 Require annual renewal of licenses to sell tobacco.
- 2.7 Increase the financial penalties for selling tobacco to persons under 18 years old and add license revocation for a fourth offense.
- 2.8 Promote understanding of the impact of tobacco price increases on use and health.
- 2.9 Increase the price of cigarettes.
- 2.10 Create zones surrounding schools and residential communities without tobacco advertising.
- 2.11 Publicize the organizations that have smoke free policies and activities.

Table 2.—Draft objectives and strategies for the community groups channel

Objective 3

By 1998, statewide community groups that serve or represent youth, women 18-35, men 40 and older, and minority groups will be involved in ASSIST activities.

Strategies:

- 3.1 Increase the number of youth, women and minority organizations that sponsor or participate in tobacco control activities.
- 3.2 Seek alternatives to tobacco sponsorship or support of events offered by community groups. Pay particular attention to community-sponsored sports events.
- 3.3 Increase the number of churches, social service agencies, community health centers and community mental health centers, senior centers, women's shelters, and group homes that offer smoking cessation programs and limit smoking to selected areas.

smoking cessation, most recently on programs for the workplace and the physician's office.

These efforts and the determination of many to lead healthier lives have led to a steady decline in smoking in Rhode Island, especially among the better educated. About half of smokers have quit.

Nonetheless, much needs to be done. More than 220,000 Rhode Islanders smoke, and many more breathe environmental tobacco smoke (ETS). We need to make tobacco use less acceptable, to enforce and strengthen existing restrictions on ETS exposure, and to make tobacco less accessible to minors. Smokers need persistent messages to quit and help in quitting. Cues to smoking, especially those which entice youth, must be restricted or eliminated. Finally, less educated smokers, unreached by messages aimed at the general public, require special interventions.

ASSIST: A New Resource

In 1991 the National Cancer Institute awarded a 7-year contract to the RI Department of Health to reduce the number of adults in the state who smoke to no more than 17% by 1998. The American Cancer Society is a partner in the project, providing a full-time staff person to work with ASSIST staff. The Rhode Island Lung Association and the Rhode Island Affiliate of the American Heart Associ-

Table 3.—Draft objectives and strategies for the worksites channel

Objective 4

Rhode Island will increase to 100% the employers of 100 workers or more who have smoke-free workplace policies, and increase the number of smaller companies that are smoke-free.

Strategies:

- 4.1 By 1998, solicit the support and cooperation of business groups and unions for smoke-free policies with special emphasis on health care, food service, retail and manufacturing worksites that employ the four ASSIST priority groups.
- 4.2 By 1998, encourage organizations that provide worksite health promotion to develop smoke-free policies, and promote those that offer policy advice.
- 4.3 By 1998, train employers and employees to enforce smoke-free policies.
- 4.4 By 1998, support employers who assist employees with smoking cessation, and encourage employers to identify a resource person in the company who can refer employees to smoking cessation services.

Table 4.—Draft objectives and strategies for the schools channel

Objective 5

Ensure enforcement of smoke-free schools legislation by 1994.

Strategies:

- 5.1 Develop and distribute a guide to enforcement of the smoke-free schools.
- 5.2 Organize a tobacco control committee of the state PTA to involve PTAs in community smoke-free activities and the importance of parent modeling of their children's smoking.

Objective 6

Amend the state health education law to increase the number of hours of health (independent of physical education) taught annually in each class K-12 by 1998.

Strategies:

- 6.1 Educate legislators to the need to change the law.

Objective 7

Increase the number of teachers who have received training in teaching health, including tobacco control.

Strategies:

- 7.1 In conjunction with the Department of Education, arrange and hold teacher training in health education.
- 7.2 Increase the number of teachers who teach health who have been certified in health education.

Objective 8

Support the provision of self-help materials and referral guidelines for students, teachers and staff who smoke.

Strategies:

- 8.1 Train Tobacco Free Teens facilitators for each high school.

ation also make significant contributions to ASSIST activities.

By the end of the project, Rhode Island should see a significant improvement in the quality of air in public buildings and public conveyances. There should be no places where minors can buy tobacco. Cigarettes will cost more. The public will know more about the ill effects of tobacco use and the value of limiting tobacco use. Any smoker who wants help with quitting will know where and how to get that help; ASSIST will promote cessation programs already in place and those developed in response to increased demand.

The Project ASSIST Organization

Rhode Island's ASSIST coalition includes health agencies, insurers, social and health service providers, businesses,

and local governments. Working in task forces, the coalition has drafted a statewide ASSIST plan and will participate in activities to reach the plan's objectives.

An executive committee, including representatives of the Cancer Society, the Lung Association, the Heart Association, and the health department, defines policy and assures proper execution of the ASSIST contract and the ASSIST plan. A steering committee, including the chairs of the four task forces and the co-chairs of the executive committee, will coordinate program activities as the ASSIST plan is implemented.

The ASSIST Plan

The ASSIST plan is a 5-year blueprint for Rhode Island's ASSIST program and is based on the NCIACS model for tobacco use prevention and cessation in the US, and contingent upon funding from

Rhode Island Medicine

Table 5.—Draft objectives and strategies for the health care settings channel

Objective 9

At least 75% of primary medical, dental, nursing, pharmacy, and other health care providers in Rhode Island will routinely advise patients to stop smoking and will provide assistance and followup so patients can do so.

Strategies:

- 9.1 Train primary care physicians, obstetricians, pediatricians, dentists, and their office staff members and pharmacists to ask patients if they smoke and to offer assistance to those who want to stop.
- 9.2 Increase the number of insurers offering materials, programs, and incentives for quitting to enrollees who smoke.
- 9.3 Reduce the number of pharmacies that display point of purchase cigarette advertisements.
- 9.4 Increase the number of pharmacies that distribute "no-smoking" literature, program lists, and smoking control products to customers who smoke.
- 9.5 Ensure that all clinics collaborating with the Rhode Island Department of Health provide access to smoking cessation, or direct services for smoking cessation.

Objective 10

All public health facilities will have enforced smoke-free policies.

Strategies:

- 10.1 Assure that clinics collaborating with the Rhode Island Department of Health have smoke-free policies and regulations.
- 10.2 Train administrators, staff and board members on how to enforce smoke-free policies in the clinics.

these two organizations. The following ASSIST plan is a draft, representing the collective ideas of the ASSIST coalition. Its final structure will evolve out of the perceived needs of the coalition over time.

The ASSIST plan is founded on 10 objectives to be achieved by reaching Rhode Islander through five channels:

- community environment;
- community groups;
- work sites;
- schools; and
- health care settings.

Additionally, the ASSIST coalition

has identified groups for whom special efforts will be made: youth, women ages 18 to 35, men ages 40 and over, and members of minority populations.

Youths were chosen as a special focus of prevention efforts because most smokers adopt the habit before adulthood. The other three groups were chosen for cessation efforts because each has been the target of tobacco industry advertising and includes a high proportion of Rhode Island's smokers.

Draft Assist Objectives

Community Environment (Table 1)

Recognizing that smoking is stimulated and reinforced by its acceptance in communities throughout Rhode Island, the objectives and strategies for this channel were selected by the ASSIST coal-

tion to counter the vision of smoking as a glamorous activity. Two types of cues are addressed, those that come from seeing people smoke in public places and those that come from advertising. Special emphasis will be placed on activities in minority communities, where some people have limited English language ability and outdoor tobacco advertising is especially focused. Enhancing the knowledge of state and local decision-makers about current tobacco control concerns will also receive special emphasis.

Community Groups (Table 2)

While the community environment is essential for controlling tobacco use, many smokers and potential smokers are members of groups that may adopt to-

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tobacco control policies and engage in tobacco control activities. Community groups may also organize community efforts to achieve tobacco use prevention and cessation objectives. Of all the organizations to which Rhode Islanders belong, sports teams, social clubs, churches, and social service providers will receive special attention, because they are especially useful in reaching the four priority groups.

Worksites (Table 3)

Because 90% of employers with 100 or more workers have smoking restriction policies in accordance with state law, they can serve as models to smaller companies. ASSIST will focus attention on certain industries, either because they employ large numbers of Rhode Islanders (health care, manufacturing, trades, crafts), or because they employ large numbers of people in the four priority groups (food service and retail).

Schools (Table 4)

The school channel, including all grades from kindergarten through high school, is most important for students, but messages about tobacco use are brought home to parents. Rhode Island is

one of seven states with laws requiring all schools to be smoke-free. ASSIST will work with school districts as they enforce the law. The state requires that health, including the health effects of tobacco use, be taught in all grades, and ASSIST will work to assure that sufficient time is spent teaching health to be effective and that teachers receive the appropriate training to teach health. ASSIST will work to make smoking cessation programs accessible to all youthful smokers.

Health Care (Table 5)

Health care was cited by coalition members as the most important channel for women ages 18 to 35, as a very important channel for members of minority populations, and of some importance for men ages 40 and over and youth. Rhode Island is the home of a research project entitled "Physicians Counseling Smokers," scheduled for completion at the end of 1993. ASSIST will help expand this successful project throughout Rhode Island. Pharmacies are a leading source of cigarette sales, even though the American Pharmaceutical Association's code of ethics discourages the practice. ASSIST will work with pharmacies to reduce the promotion of

tobacco use. Community clinics are an important source of health care to women ages 18 to 35 and members of minority populations, two of ASSIST's priority groups. The health department will work with its clinic partners to effect smoke-free policies and provide patients with smoking cessation services.

Conclusion

Rhode Island is well on the way to becoming a smoke-free society. The ASSIST plan is designed to facilitate this process. You can help by contacting Project ASSIST (277-3293) or the drug abuse prevention task force in your community (call 454-7210 for the number of your task force), and by supporting ASSIST activities as they are fielded. You can also encourage the organizations to which you belong to have smoke-free policies and to sponsor events that encourage not smoking.

Address correspondence to:
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RI Department of Health
3 Capitol Hill
Room 103
Providence, RI 02908-5097

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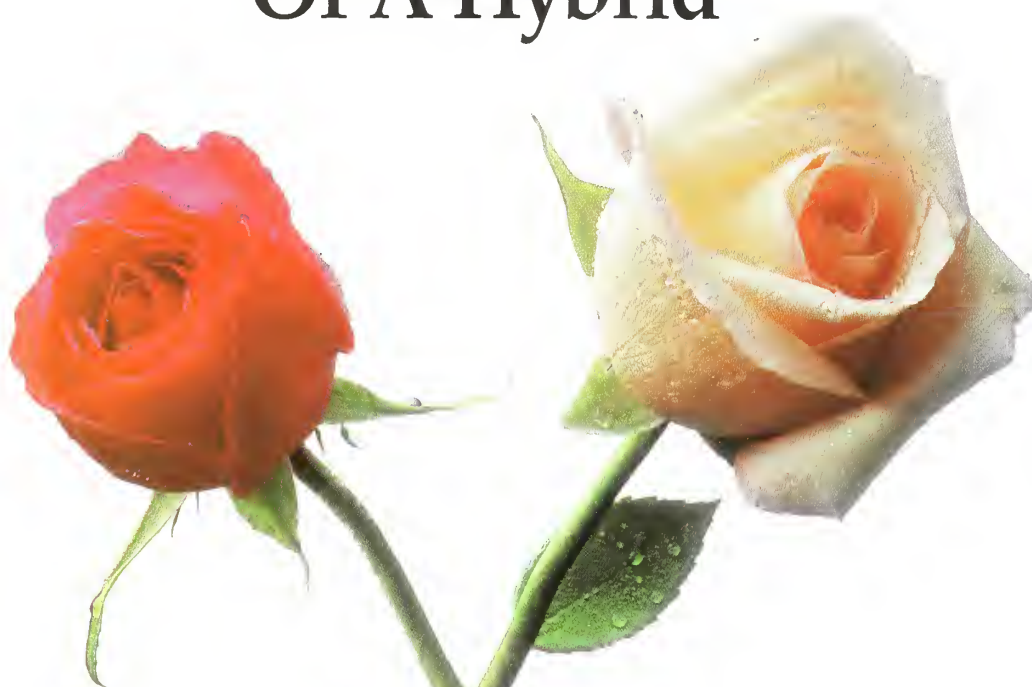
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USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

VASERETIC® 10-25
Enalapril Maleate-Hydrochlorothiazide

Next

Dosage must be individualized; the fixed combination is not for initial therapy.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, see adjacent pages.

VASERITIC (ENALAPRIL MALEATE/HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY. When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERITIC (Enalapril Maleate/Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal Neonatal Morbidity and Mortality*.

CONTRAINDICATIONS. VASERITIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS. *Congenital Deformities.* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt-volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERITIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema. Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERITIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided. (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Neutropenia/Leukopenia. Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide. Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions*). Enalapril Maleate and Hydrochlorothiazide.

Pregnancy. *Enalapril Hydrochlorothiazide.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 times the maximum human dose) or mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses, 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERITIC should be discontinued as soon as possible (see Enalapril Maleate/Fetal Neonatal Morbidity and Mortality below).

Enalapril Maleate/Fetal Neonatal Morbidity and Mortality. ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Premature, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester could be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERITIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no

10 mg



25 mg

alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intrauterine environment.

If oligohydramnios is observed, VASERITIC should be discontinued unless it is considered essential for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Infants, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide. *Reproduction.* Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4, 5, 6 mg/kg/day (approximately 1-2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Neutropenia Effects. These may include leuko and/or neutropenia, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS. *General.* Enalapril Maleate. *Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with an angiotensin converting enzyme inhibitor, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients. Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia. Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.2 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia in renal renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril (see Drug Interactions).

Cough. Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia. In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide. Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuretics, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia, and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see Drug Interactions, *Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the

treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypernatremia may occur or frank edema may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-symptomatic patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Interactions with Patients. *Angioedema.* Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension. Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia. Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERITIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions. Enalapril Maleate, *Hypotension—Patients on Diuretic Therapy.* Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS).

Agents Causing Renin Release. The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents. Enalapril has been used concomitantly with beta-adrenergic blocking agents, methyldopa, nitrates, calcium-channel agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium. Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium. Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE-inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium. Hydrochlorothiazide. When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics. potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs.—additive effect or potentiation.

Cholestyramine and colestipol resins. Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids. ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pseudo amines (e.g., norepinephrine). possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants. *nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant.

Lithium. should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERITIC.

Non-steroidal Anti-inflammatory Drugs. In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERITIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse

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bone marrow assay

Enalapril Maleate. There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively (15 and 300 times the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: re-assay, reverse mutation assay with *L. coli* sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vitro* cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide. Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 800 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatic carcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes (Chinese hamster bone marrow chromosomes) and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell mutagenicity assays using concentrations of hydrochlorothiazide from 470 to 1300 µg/ml and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies where these species were exposed via their diet to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy. *Pregnancy Category C* (first trimester) and *D* (second and third trimesters). See WARNINGS, *Pregnancy*, *Enalapril Maleate*, *Fetal/Neonatal Mortality and Morbidity*.

Nursing Mothers. Enalapril and enalapril are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. VASERETIC has been evaluated for safety in more than 1500 patients, including over 800 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent) and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 20 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain, *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia, *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth, *Genitourinary:* Impotence, nocturia, priapism, decreased libido, *Neurological:* Vertigo, *Skin:* Pruritus, rash, *Other:* Dyspnea, goiter, back pain, arthralgia, diphtheria, decreased libido, tremors, urinary tract infection.

Angioedema. Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension. In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.8 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough. See PRECAUTIONS, *Cough*.

Chemistry. See Laboratory Test Findings, *Serum Electrolytes*. See PRECAUTIONS.

Concomitant Blood Urea Nitrogen. In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium. See PRECAUTIONS.

Hemoglobin and Hematocrit. Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests. Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Other adverse reactions that have been reported with the individual components are listed below, and within each category, are in order of decreasing severity.

Enalapril Maleate. Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*), *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*), pulmonary embolism and infarction, pulmonary edema, rhythm disturbances including atrial tachycardia and bradycardia, atrial fibrillation, hypotension, angina pectoris, *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic), jaundice, melena, anorexia, glossitis, stomatitis, dry mouth, *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported, a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g. paresthesia, dysesthesia), *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia, *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity, *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Vasculitic. A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia, arthritis, myalgia, myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Mortality and Morbidity. See WARNINGS, *Pregnancy*, *Enalapril Maleate*, *Fetal/Neonatal Mortality and Morbidity*.

Hydrochlorothiazide. *Body As A Whole:* Weakness, *Digestive:* Pancreatitis, jaundice (intrahepatic, cholestatic, jaundice), salivary gland, cramping, gastric irritation, anorexia, *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia, *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angitis, vasculitis, and cutaneous vasculitis, fever, respiratory distress in lung pneumonitis and pulmonary edema, anaphylactic reactions, *Musculoskeletal:* Myositis, *Nervous System/Psychiatric:* Restlessness, *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS), *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia, *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubiaceae and related trees. Also in *Rauwolfia Serpentina* (L.) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

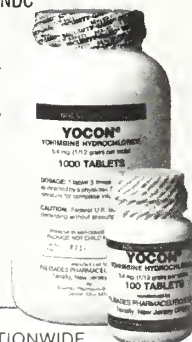
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

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Smoking Control at the Workplace:

Current Status and Emerging Issues

Laura A. Linnan, MEd, Karen M. Emmons, PhD, Edward C. Galuska, CISW, David B. Abrams, PhD

Cigarette smoking accounts for about 434,000 deaths in the US every year, 1 in 7 deaths overall and more than all deaths due to cocaine, heroin, alcohol, acquired immunodeficiency syndrome (AIDS), fire, suicide, homicide, and auto accidents combined.¹ However, the risk is not limited to smokers. The Environmental Protection Agency recently ruled that environmental tobacco smoke (ETS) is a Group A carcinogen responsible for excess morbidity and mortality related to respiratory disease and lung cancer among healthy nonsmokers.² ETS is particularly problematic at the workplace.³

Employer Motivations for Supporting Smoking Control at the Workplace

Corporations have shouldered an increasing burden of the cost of health care during the last 2 decades. Currently, 14% of the gross national product is spent on health care alone.⁴ The average annual cost of an employee health plan is \$3,573, more than double the cost in 1985. Without intervention, health care costs will

continue to rise 12% to 13% over each of the next 5 years, with staggering implications for businesses, workers, health care providers and the government.

Health care costs consume an estimated 26% to 46% of the business profit margin. Both management and employees are anxious to find ways to control these costs. Self-insurance, pre-certification, increased employee cost-sharing, case management, utilization review and preferred provider arrangements are all strategies that are being applied to address health care costs.

Wellness programs that contain both primary and secondary prevention efforts are designed to detect problems at an early stage or prevent the occurrence of disease altogether have also been increasingly employed. Also, employee assistance programs (EAPs) are now combining alcohol and drug prevention with general wellness programs that include tobacco control, exercise, dietary change, and stress management. For example, Du Pont Corporation analyzed the impact of seven key risk factors on absenteeism and health care costs for its US workforce of 96,000. Employees who smoked had 24,538 excess illness days and a total excess illness cost of more than \$26 million. This translates to an annual excess illness cost of \$960 for each smoker.⁵ In addition, smokers averaged 6 more health care visits per year than nonsmokers, and dependents of smokers averaged almost 4 visits more per year than dependents of nonsmokers.⁶

Besides the obvious decrement in quality of life and the disproportionate contribution of smoking to chronic disease, death and disability, the health care bill of smokers are prime motivators for business leaders to support smoking control programs. Several additional compelling arguments have been raised in support of workplace smoking control efforts:

Employee productivity affects profits. Research indicates that smokers are absent 33% to 50% more than non-smokers.^{6,7} Work disruptions also decrease

... smokers averaged six more visits in the health care system per year than nonsmokers, and dependents of smokers averaged almost four more health care visits than did dependents of nonsmokers.

productivity, and about 8% of a smoker's work day is spent smoking.^{6,8}

Top management now recognizes smoking's risk to health. An independent poll of executives ranked smoking control first on a list of cost-beneficial health promotion programs.⁹ Cigarette smoking was ranked second only to back injuries on the list of the five health problems that affect workforce health most seriously.¹⁰

Employers are responsible for maintaining a safe and healthy work environment. Smoking can be a fire and safety hazard. With the recent classification of ETS as a Group A carcinogen, employers who allow smoking in the workplace are now putting themselves at risk for litigation. Employers have an obligation to limit worker exposure to ETS, as they do with asbestos, and other known occupational carcinogens.

*Shimp vs New Jersey Bell*¹¹ was the first legal victory assuring an employee's right to protection from ETS exposure. It is anticipated that a whole new wave of litigation will follow. Many states and local jurisdictions already have established regulations regarding smoking in public places and in the workplace. In Rhode Island, the Workplace Smoking Pollution Control Act of 1986 requires all businesses to implement and enforce a workplace smoking policy for their employees. Nationally, all hospitals who wish to remain accredited by the Joint Commission on Accreditation of Health Care Organizations (JCAHO) must comply with a smoking ban by 1994. Hospitals are important influences on the health

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ABBREVIATIONS USED
AIDS: Acquired immune deficiency syndrome
EAP: Employee assistance program
EPA: Environmental Protection Agency
ETS: Environmental tobacco smoke
JCAHO: Joint Commission on Accreditation of Health Care Organizations

behavior of their employees, patients and visitors and can serve as role models for workplaces that are moving toward restrictive policies. Hospitals play a critical role in achieving the goal of a smoke-free society by the Year 2000.

Employee Motivations for Supporting Smoking Control at the Workplace

The proportion of adult smokers in the US has dropped dramatically in the last 3 decades from 40% in 1965 to 27% today. More than 44 million smokers have quit the habit.

The percentage of smokers in the workplace tends to reflect national trends, but worksites with predominantly blue collar or lower income employees tend to have prevalence rates of 40% to 55%, trends are consistent with national surveys. Since non-smokers are in the majority, support for smoking policy restriction tends to be high.¹² With growing attention to the dangers of ETS, the "silent" majority of nonsmokers soon may become much more vocal. Women and minorities are particularly important segments of the smoking population because cessation opportunities have not adequately addressed their needs, and they are targets of aggressive advertising by the tobacco industry. The workplace is an ideal setting to gain access to many smokers who would be difficult to reach by other channels.

Business leaders and employees have many sources of support for smoking control efforts at the workplace. The public health community has learned a great deal since the first US Surgeon General's Report was released in 1964 about how to combat the powerful tobacco industry. Researchers have worked diligently and effectively to help bring products and services to the marketplace that assist smokers in their efforts to quit. Health care providers such as physicians, nurses, health psychologists, pharmacists, dentists along with risk management professionals, benefits directors, top management and others, are playing an increasingly important role in delivering or supporting cessation opportunities and policy changes.

Evolution of Workplace Smoking Control Activities

Early workplace smoking cessation programs tended to be one-shot interventions where professionally led staff from a clinic, voluntary health agency or re-

search program simply replaced their original location with the workplace. The behavior modification approach usually consisted of 6 to 8 weekly meetings of 1 hour each, with 8 to 12 smokers who were ready to quit. Extensive reviews of the literature prior to 1982 found that these early efforts were under-researched, not well controlled, had few measurable outcomes (beyond self-report), and did not consider any of the policy or environmental conditions that may have influenced outcomes.¹³ Such programs influenced fewer than 10% of the smokers at the workplace, and of those, only about 30% would remain abstinent after a year.

In addition, professionally led clinic programs were relatively costly, which reduced their accessibility to most employees. Many worksites were not willing to offer programs on company time, so participation was further limited. Smaller and moderate size worksites experienced additional barriers since there would be few smokers interested in quitting at any one particular moment in time when a program was offered. The latest thinking about workplace smoking programs is to focus on both the individual and the organizational environment to achieve a sustained and long-lasting approach to reducing or eliminating smoking at the workplace over a period of years.¹³

Individual Change Programs

Early worksite programs were based on the premise that most smokers were motivated to quit smoking and that they needed assistance in developing the skills necessary for success. These action-oriented, skills-based programs attracted only a small percentage of the smoking population.

Recent research suggests that over 90% of smokers in workplace settings are *not* ready to quit smoking.¹⁴ Theoretical advances suggest that there are stages of motivational readiness to quit smoking that represent a long-term, dynamic process. Individuals can be characterized on a dimension of motivation or readiness to quit, ranging from not at all ready (precontemplation), to successfully having quit and maintaining abstinence (maintenance).

The Transtheoretical Model of stages of change (see Prochaska in this issue) illustrates the need for a multi-faceted approach to smoking control programs. For example, individuals in the early stages of readiness would not be interested in traditional cessation programs but might be open to educational informa-

tion or health-related assessments such as pulmonary function testing. Since most smokers are *not* ready to quit, efforts to accelerate movement through the stages of readiness are essential.

Since the early 1980s Miriam Hospital's Division of Behavioral Medicine has been conducting research on smoking in the workplace. Abrams and Biener (1989) report preliminary results of a study involving 6 Rhode Island worksites. The study investigated a sustained, multi-component approach to worksite smoking control that targeted both the individual and the organizational environments. The program lasted 12 months and included multiple, novel, and repeated offerings of a variety of interventions targeting all stages of readiness to change. Individual level interventions included lung function and carbon monoxide tests, monetary incentives for 24 hours of abstinence, site-wide competitions for longer term abstinence, self-help programs, educational materials, and more traditional group smoking programs with and without nicotine gum and behavior modification. In addition, consultations were provided with top management regarding smoking policy. In the experimental worksites, the overall smoking prevalence was reduced by 14.2%, compared to 8.9% at control worksites. It should be noted that the usual quit rate in the general population is about 1% to 3% per year. The intervention program seemed to have the most impact on male blue-collar workers, who had a four-fold increase in quit rates over those found among their counterparts in control worksites. If a 14% per year cessation rate could be sustained over time on a population-wide basis, the public health impact would be massive.

These results have been replicated and extended by other researchers nationally.¹⁵⁻¹⁷ A recent meta-analysis of 20 well-controlled workplace-based research studies conducted to date revealed that worksite interventions do produce significant improvements in outcomes compared to controls.¹⁸ The overall average cessation rate was 13% at 12-month follow-up. It is generally agreed that: 1) clinic-based and self-help programs can be successfully conducted at the workplace; 2) incentives, competitions, and other organizational interventions can enhance motivation, recruitment, and participation rates; and 3) social pressures and social norms from both smoking and nonsmoking coworkers are strongly associated with smoking attitudes and some behaviors.^{13,19}

Environmental Change Programs

Because of its powerful influence on social norms, the organization plays a key role in smoking control interventions. The ideal goal is to engineer change in the worksite's social and physical environment to be maximally supportive of healthier lifestyles. Restrictive smoking policies at the workplace have been shown to decrease nonsmokers' exposure to ETS,²⁰ to modify social norms, to reduce smokers' cigarette consumption during working hours,¹² and in some studies, to increase smoking cessation.²¹ Social norms have been directly related to individual smokers' motivation to quit.¹⁴

At the organizational level, the current status of the worksite can be assessed by means of a needs assessment or survey of workers and management. This could be smoking-specific or part of a broader health-risk appraisal for chronic disease prevention. Attitudes, knowledge, interest and behaviors of management and employees about smoking, ETS, and policy restrictions may be determined. Feedback to management and employees can then be used as the basis of creating increased awareness of the need to improve the social and physical environment of the worksite. Program evaluation can assess results of intervention programs offered and feedback can be provided to illustrate the organization's progress.

The Future

The first national worksite survey conducted in 1985 revealed that 66% of worksite respondents had offered at least one health promotion program, and 36% of these had offered some type of smoking cessation materials or program. In 1992, a follow-up nationwide survey determined that 81% of all responders had offered at least one health promotion program. Of those, 40% had offered information or activities to help employees stop smoking.

The larger the size of the worksite, the more likely they were to have offered some type of health programming. In 1985, 27% of responding worksites had a smoking control policy that prohibited or severely restricted smoking in the workplace; this grew to 59% in 1992.²² The Year 2000 Health Objectives for the nation expects to increase to at least 75% the proportion of worksites with 50 or more employees with a formal smoking policy that prohibits or severely restricts smoking at the workplace.

A 1992 American Cancer Society

survey of small (50 to 250 employees) manufacturing worksites in Massachusetts found that 25% of all responders indicated that smoking was not allowed anywhere (or only allowed outdoors).²³ The smallest worksites (50 to 149 employees) were much less likely to have restrictive smoking policies. A promising finding was that stop-smoking programs were the health promotion program most likely to be offered by small worksites and were first on the list of programs likely to be offered in the next 12 months.

The following strategies for the future may help meet the challenges before us.

New Technologies.—Computer databases and expert system technology allows employees to stop by a computer terminal or laptop, complete a menu-driven series of questions, and be "staged" according to their readiness to quit smoking. Based on responses, they will be given feedback, materials or information to help move them along the processes of quitting. Feedback, support and reminder messages may also be built into the on-screen programming. While the technology of using menu-driven educational messages has been used in other applications previously, it is relatively new to smoking cessation. A central database can keep track of all sources of health care costs and utilization to further enhance control over cost and target high use groups with preventive services. Computer-based systems may be the wave of the future for wellness programs in general.

Pharmacological Advances.—The nicotine patch and other pharmacologic aids have gained widespread attention in the past 2 years. Such programs are more effective when a strong behavior modification program is included. A physician prescription is required, so employees may learn about the patch through programming or information at the workplace. New research into nicotine inhalants may make these products available in the marketplace soon. The workplace and medical professionals can serve as an important channels for sharing information about the newest pharmacological advances and can provide adjunct therapies such as behavior modification programs to support those who use new treatments to enhance success rates in the future. Health insurance plans are increasingly willing to cover programs with demonstrated efficacy such as combined pharmacological and behavior modification strategies.

Collaboration with Physician Net-

works.—Very few small or medium-sized businesses have access to on-site physician services. Future smoking control efforts may involve better collaborations between the business and physician communities. Contract services for pre-employment or periodic physical examinations may include services to enhance smoking control efforts. Collaborations between hospital-based wellness providers and industry are becoming more commonplace in the 1990s.

Insurance carriers may contract with physician providers to write prescriptions for pharmacological aids that give easier access to employees. Employees have indicated that if they needed, wanted or were required to attend a smoking cessation program, they would prefer having a physician involved and prefer to attend in a medical setting or at the worksite.⁶ When physicians are involved in cessation programs many other creative arrangements are possible to improve the likelihood of successful outcomes.^{24,25}

Multiple Risk Factor Approaches.—Early stage individuals are reluctant to think about making changes in their smoking habits. Successful workplace smoking cessation programs of the future will use "back-door approaches" to motivate these individuals to consider making a change. For example, blood cholesterol screenings are popular activities that may draw up to 50% to 90% of an employee population. Smokers who are counselled about their blood cholesterol results, whether in person or in writing, should get a strong message about quitting smoking. In addition, employees who successfully change one risk factor may be more motivated to make changes in other behaviors, such as smoking. Our research agenda at the Miriam Hospital Division of Behavioral Medicine is aggressively moving to study these associations. As more companies move toward offering comprehensive wellness programs that include exercise, diet, and stress management, smoking cessation messages may be integrated. These reinforcing, yet more subtle cues to action, may prove to be powerful motivators, especially for early stage smokers.

Case Management of High Risk Employees.—Future smoking control activities at the individual level may involve the identification of high-risk employees and intensified treatment efforts. The evidence is that about 20% of those covered by insurance account for 80% of health care costs. Often these employees (or their dependents) have multiple life-

style problems including chronic diseases, alcoholism, obesity and sedentary lifestyles. Employers will be identifying individuals who submit a high number of health care claims. These individuals are likely to be smokers²⁶ and may receive referrals to clinic-based programs at the worksite or sponsored at some offsite location. For example, the Miriam Hospital's Division of Behavioral Medicine - Nicotine Dependence Program offers outpatient individual and group smoking cessation treatments. Individual patient assessment and treatment offerings can serve both the general public and business community.

Benefits Re-Design.—Many fire, disability, life and health insurance companies are now offering premium reductions to employers who maintain a smoke-free environment. Even self-insured businesses now recognize the cost-savings of employing fewer smokers. An emerging trend is the re-designing of benefits packages to either reward non-smokers with incentives or to penalize smokers with surcharges. For example, Baker-Hughes, Inc., a Houston-based oil field equipment manufacturer rates employees' risk and adds a \$10 a month surcharge for tobacco users onto the health insurance premium. In addition, the deductible is waived for all employees who pass 3 of 4 wellness checks (cholesterol, blood pressure, height/weight and triglycerides), and \$100 is deposited into a tax-free account that can be used to pay out-of-pocket health care costs.²⁷ As many as 15% of employer respondents to a recent survey indicated that incentives or penalties would be included in benefits packages to encourage employee participation.²⁷ As health care costs continues to rise, we anticipate more benefits restructuring that support smoking control efforts. Future trends in benefits designs will also include dependents who are covered by employee health care plans.

Total Smoking Bans Implemented.—The EPA report has already sparked a great deal of interest among employers, even those who have been slow to respond to the scientific evidence and public outcry surrounding environmental tobacco smoke. Since employers may be held liable for exposing employees to a cancer-causing agent, we anticipate a dramatic increase in the implementation of severely restrictive smoking policies or total smoking bans at the workplace.

Conclusion

Worksite and medical professionals can contribute significantly towards the

national objectives of a smoke-free society. As part of the larger community, we predict that the workplace will serve as an important role model in the movement toward smoke-free communities. Buoyed by the facts that surround environmental tobacco smoke, and the cost of smoking to business and the larger community, business leaders will unite with health care providers, insurance carriers, government agencies, researchers and voluntary health agencies who have taken up the fight to clear the air. Americans are spending many hours at the workplace where smoking is being limited. Tighter restrictions are now placed on smoking in schools, retail establishments, on public transportation, in restaurants and in health care settings. Children are being taught to avoid smoking initiation at earlier ages, and advocates for smoke-free

establishments are gaining wider acceptance. Government-funded projects like Rhode Island's Project ASSIST will promote smoking control efforts through numerous channels including schools, worksites, physician offices, legislation and the media. The workplace will continue to be an important player in these community-based initiatives.

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The Role of Primary Care Physicians In Smoking Cessation

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The Surgeon General has stated that "smoking is the chief avoidable cause of death in our society."¹ Because the majority of smokers will visit a physician at least once each year, physicians can play a central role in reducing the morbidity and mortality associated with cigarette smoking. Although physicians generally recognize the importance of smoking cessation as a disease-preventive measure, few physicians are confident in their ability to help patients stop smoking.^{2,3} Moreover, fewer than half of smokers report that their physicians have ever advised them to quit smoking.^{4,5}

In this article, we will first discuss the reasons why primary care physicians are especially well-suited for providing smoking cessation interventions to their patients (Table 1). Then, we will review recent data on the status of physician involvement in smoking cessation interventions and outline the barriers to the provision of these interventions in primary care settings. Finally, we will outline specific strategies to help primary care physicians and their office staff overcome these barriers and provide effective interventions to their smoking patients.

The Role of the Primary Care Physician in Smoking Cessation

More than 70% of smokers contact a physician each year, and each smoker averages more than 4 visits per year.⁶ During many of these encounters, the

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patient is likely to have an acute or chronic medical problem that is related to smoking. These "teachable moments" are times when patients may be most receptive to smoking cessation advice or intervention. Even if the patient is asymptomatic, physicians can link the patient's smoking to increased risk for disease in the future (eg, heart disease if the patient has a family history of early coronary artery disease). Moreover, the recent widespread adoption of smoke-free

Table 1.—Smoking Cessation in Primary Care—Why Primary Care Physicians?

70-75% of smokers see physicians at least once a year
Multiple opportunities to intervene over time
Teachable moments
Physician-delivered interventions are effective
Physician-delivered interventions are cost-effective
Opportunity to involve office staff/ utilize office systems
Opportunity to utilize pharmacologic interventions

policies in hospitals and other health care institutions provide additional new opportunities for physician intervention.

Perhaps the most compelling reason to focus on physician-delivered smoking cessation interventions is that they are effective.⁷⁻⁹ Research has demonstrated that even brief physician advice alone more than doubles 1-year smoking abstinence rates when compared to controls, while the addition of physician training, educational materials, pharmacologic aids and follow-up visits further increases the effectiveness of physician-delivered interventions.⁷⁻¹⁰

In a meta-analysis of 39 controlled trials of smoking cessation interventions in medical practice, patients who received smoking cessation interventions had 5% to 8% higher 1-year abstinence rates than controls.⁷ Intervention from both physicians and non-physicians and the use of multiple modalities to provide individualized advice on multiple occasions pro-

... the most compelling reason to focus on physician-delivered smoking cessation interventions is that they are effective.

vided the best result 6 months after the initiation of the intervention.⁷ Recent studies have shown that physician-delivered smoking cessation interventions are most likely to be effective when trained physicians are routinely reminded to intervene with all smoking patients—by chart stickers or similar reminder systems,⁸ or when office staff are used to support smoking interventions.^{11,12}

Physician-delivered smoking interventions are not only effective, they are cost-effective, especially when compared to such accepted medical practices as the treatment of mild to moderate hypertension or hypercholesterolemia.¹³ Cummings and colleagues performed a cost-effectiveness analysis of brief physician advice and follow-up visits for smoking cessation.¹³ Using a very conservative estimate of the effectiveness of brief advice (2.7% increase in 1-year smoking abstinence rates) the cost per year of life saved (YLS) was \$740.¹³ This compares with costs of more than \$11,000 per YLS for treating hypertension and more than \$65,000 per YLS for treating moderate hypercholesterolemia.¹³ Even if physician advice only produced a 1% increase in 1-year smoking abstinence, the cost per YLS (\$2,020) would be less than 5 times that of treating hypertension and less than 30 times that of treating moderate hypercholesterolemia.¹³ Adding a single smoking counseling follow-up visit, assuming an additional 1% increase in 1-year smoking abstinence, costs \$5,051 per YLS, still well below the cost of accepted preventive practices.¹³

Physicians also have the opportunity to prescribe pharmacologic interventions for the treatment of smoking cessation. Nicotine replacement strategies (ie, nicotine resin complex, nicotine transdermal patches) are effective as interventions for smoking cessation when used in conjunction with behavioral interventions.¹⁴⁻¹⁶ Though placebo-controlled trials in the medical setting have found

ABBREVIATIONS USED

*NCI: National Cancer Institute
YLS: Years of life saved*

Table 2.—Organizational Factors that Enhance the Provision of Effective Smoking Cessation Interventions in Primary Care^{33,49}

Screening and labeling of smokers
Prompts and reminders
Orientation and training of physicians and staff
Resources
Self-help materials
Counseling guides and manuals for physician and staff
Referral options
Policy establishment with staff endorsement
Coordination and implementation of intervention and follow-up plans
Maintenance program
Audits with feedback
Team-building and incentives
Repeat orientation and training

that nicotine gum is not significantly more effective than placebo in enhancing long-term abstinence, several studies performed in the medical and dental setting have found that nicotine gum is significantly more effective than no gum treatment conditions.¹⁶ Nicotine transdermal patches have not been widely tested in the primary care setting, but at least two European studies have found that they are more effective than placebo when combined with minimal adjuvant therapy in general medical settings.^{17,18}

Status of Physician-Delivered Smoking Interventions

Though physicians recognize the importance of smoking cessation as a preventive health measure, few physicians are confident in their own ability to help patients stop smoking.^{2,3,19-21} Though 75% to 90% of primary care physicians report that they provide smoking cessation advice to all or almost all of their smoking patients,^{3,20} population-based patient surveys indicate that only a relatively small percentage (44% to 51%) of smokers report ever having been advised to quit smoking by a physician.^{4,5,22}

Quite recently, a population-based sample of 4296 Rhode Island smokers was obtained for a longitudinal study that will test the effectiveness of a strategy to disseminate physician-delivered smoking cessation interventions. Of the 3377 smokers who reported having contact with a physician in the past year, only 51% reported that a physician or health care provider talked with them about smoking.²³ Of these 1555 smokers, 89%

reported that they were advised to quit smoking, while only 29% stated that they were offered help in quitting.²³

According to studies using patient exit interviews to document physician behavior, only 27% to 45% of patients reported that they were advised to quit during a specific visit.²⁴⁻²⁷ Patients are more likely to receive advice if they have a history of smoking-related disease.^{25,28} Though there may be some under-reporting of smoking cessation advice on the part of patients, the results of these studies underscores the need for more physician involvement in smoking cessation interventions and suggests that many smoking patients are either not getting, not hearing or not recalling smoking cessation advice from their physicians.

Moreover, results of primary care physician surveys indicate that of those who do encourage their patients to stop smoking, few are providing a significant "dose" of an intervention. Less than 50% of physicians use a combination of strategies including counseling;²⁹ less than 50% counsel all smoking patients for more than 3 minutes at every visit;²⁰ only about 30% regularly spend 5 or more minutes counseling patients about their smoking on their first visit; 33% to 44% never help patients to set quit dates;¹⁹ 68% to 75% never make follow-up appointments with patients primarily about smoking;¹⁹ and only 15% to 25% report regularly referring smokers to quit-smoking programs or clinics.^{19,30}

How do Rhode Island physicians compare to these reported rates of counseling? A survey of 246 Rhode Island primary care physicians was conducted in 1991-1992 as a component of the Physicians Counseling Smokers Project, a National Cancer Institute-funded study to test the effectiveness of a strategy for disseminating smoking cessation interventions among Rhode Island physicians. Seventy-four percent reported that, in a typical office visit, they advise more than 80% of their smoking patients to quit; 35% reported that they provide assistance (ie, several minutes of counseling, quitting materials, pharmacologic interventions or a referral) to more than 80% of their smoking patients; while only 8% reported arranging a follow-up visit or phone call specifically for smoking to more than 80% of their smoking patients.³¹ Only 27% of these Rhode Island primary care physicians met the criteria for "thorough" counseling, defined as providing assistance at every visit, for at least 3 minutes, to all smokers regardless of health status or desire to quit.³¹

Barriers to the Provision of Smoking Cessation in Primary Care Settings

Barriers that help to explain the limited involvement of physicians in smoking cessation interventions include: limited knowledge of the benefits of physician intervention; lack of counseling skills; perceived ineffectiveness and lack of confidence; the belief that patients don't want to quit; little or no reimbursement for counseling interventions; lack of organizational support; and limited availability of materials to aid physicians and patients in smoking cessation efforts.^{9,19,20,32,33} All of these barriers are potentially addressable, however.

Lewis and colleagues²⁰ recently reported that only 28% of a random sample of internists said that they were moderately or very effective as smoking cessation counselors. Those who perceived themselves as very or moderately effective were significantly more likely to counsel for 3 or more minutes.²⁰ In another survey in nearby Massachusetts, only 12% of university hospital-based physicians and 16% of community-based physicians felt "very prepared" to counsel patients about smoking.³ On a positive note, studies that have provided physicians with training in smoking counseling skills have demonstrated an increase in skills as well as feelings of increased effectiveness.^{19,34,35}

Though lack of training, lack of effectiveness and not enough time are rated as important barriers by a majority of inter-

Table 3.—Interventions for Patients in Preparation, Action or Maintenance Stages of Change

Set a specific quit date
Write a contract
Provide self-help materials,
Prescribe nicotine replacement (when appropriate),
Teach behavioral skills
self-monitoring
goal-setting
self-reward
stimulus control
substituting alternative behaviors
relaxation exercises
coping skills training
relapse prevention skills
Identify and treat psychiatric comorbidity
Recommend an exercise program
Refer to formal treatment programs
Enhance social support

nists, more physicians rated "smokers not interested in quitting" as an important barrier than any other barrier in a recent survey. More than two-thirds of this sample also reported that "counseling about smoking is frustrating." These findings suggest that physicians feel especially unprepared and ineffective when faced with patients who are not yet ready to quit. For some physicians, these negativistic feelings are fueled by unrealistic expectations. Because even the most effective physician-delivered intervention will result in 1-year abstinence rates of less than 25%, physicians will become increasingly frustrated if they expect their efforts can produce abstinence rates of greater magnitude. This barrier may be overcome by helping physicians to develop more realistic expectations, by providing them with specific training in motivational techniques and encouraging them to focus on intermediate outcomes, such as moving a patient who is not interested in quitting to a contemplation stage, where they are thinking about quitting for the first time.⁶

Another barrier to smoking cessation counseling may be the physician's personal smoking status. In one large survey, male, but not female, internists who were smokers were significantly less likely to counsel all smokers than non-smoking physicians.²⁰ On a positive note, a recent survey of Rhode Island physicians documented a decline in the rate of current cigarette smoking from 33% in 1963 to only 4.6% in 1988.³⁶

Even when physicians are provided with specific training to overcome knowledge, skill and attitudinal barriers, the presence of organizational barriers may seriously interfere with the delivery of physician-delivered smoking cessation interventions.^{8,33,37} Kottke, Solberg and Brekke describe several essential organizational components (Table 2) that are often lacking in primary care office settings.³³ Lack of reimbursement for smoking cessation counseling is another important barrier. Though physician-delivered smoking cessation counseling and follow-up is cost-effective¹³ most third-party payers won't pay for counseling by physicians or office staff. Recently, however, there has been some movement toward coverage of smoking cessation services. In Rhode Island, Ocean State Health Plan will pay for counseling if a primary care provider documents patient participation in a structured program, but only after the patient is able to quit and stay quit for 15 months. Harvard Community Health Plan provides on-site coun-

Table 4.—Guidelines for Use of Nicotine Transdermal Patches in Primary Care

Patient selection criteria:

1. significant nicotine dependence is present:
 - smoking rate of more than 20 cigarettes per day
 - first cigarette within 20-30 minutes after arising
 - withdrawal symptoms during previous quit attempts
2. patient is in preparation or action stage (highly motivated to quit)
3. patient is willing to use self-help materials or formal program and return for follow-up

Selection of Dose:

1. highest dose for patients:
 - smoking more than 10 cigarettes per day
 - weighing more than 100 pounds
2. intermediate dose for patients:
 - smoking 10 or less cigarettes per day
 - weighing 100 pounds or less
 - elderly
 - with an acute vascular disease or event
 - pregnant women (when non-pharmacologic management has failed)

Establish a quit date—begin patch only after cessation of smoking
Discontinue patch if patient returns to smoking (more than 5 cigarettes per day)

Monitor and adjust dose for:

1. side effects or toxicity:
 - skin reactions
 - insomnia or vivid dreams
 - nausea, lightheadedness, gastrointestinal symptoms
2. breakthrough withdrawal

Duration of therapy:

1. initial dose for 2-6 weeks
2. taper to next lower dose for 2 weeks
3. taper to lowest dose for 2 weeks or discontinue

Always provide:

1. office-based counseling—"5 As"
2. self-help materials from pharmaceutical company or agency
3. follow-up visits or phone calls

seling through their health education department at very low cost. Of course, a physician always has the option of billing for a routine office visit if the patient has an associated medical condition that warrants further assessment or treatment (eg, bronchitis, hypertension).

Strategies for Effective Interventions: Understanding How People Change

Although physician-delivered smoking cessation interventions are effective, only a small minority of patients who receive interventions from physicians are successful in achieving long-term abstinence. As noted earlier, the frustration and feelings of ineffectiveness that result from these low rates of success are an important barrier to continued physician intervention with smokers. The Transtheoretical Model of Change (see Prochaska in this issue) can help physicians to assess and intervene with their smoking patients more effectively.⁶ By characterizing the stages and processes of smoking cessation, the transtheoretical model offers a strategy for intervening with the majority of smokers who are not ready to quit smoking when they visit a physician's office.

The Transtheoretical Model, developed by psychologists James Prochaska and Carlo DiClemente at the University of Rhode Island, identifies five discrete stages of smoking cessation: precontemplation, contemplation, preparation, action and maintenance (Figure 1).^{6,38} Individuals at the precontemplation stage, who may represent as many as 40% of current smokers seen in a typical medical practice, are not considering making any changes in their smoking in the foreseeable future. These patients may be uninformed or underinformed, demoralized about their ability to change, or defensive and resistant to change.

Contemplation is a stage of ambivalence that characterizes another 40% of smokers seen in a medical setting. Though individuals at this stage have given serious thought to giving up smoking, they are not yet ready. Most individuals in the contemplation stage rate the hazards of smoking only slightly higher than the benefits. Only about 20% of smokers who seek medical care are in the preparation stage and are intending to quit smoking in the next month. Many of these patients have made a quit attempt in the past year, or have taken small steps toward quitting, such as delaying their first cigarette in the morning or cutting down on the number of cigarettes that they smoke.

When individuals finally reach the action stage, they have overtly tried to quit smoking. Relapse is the rule during this stage, rather than the exception, especially during the first few days and weeks after quitting. Maintenance, de-

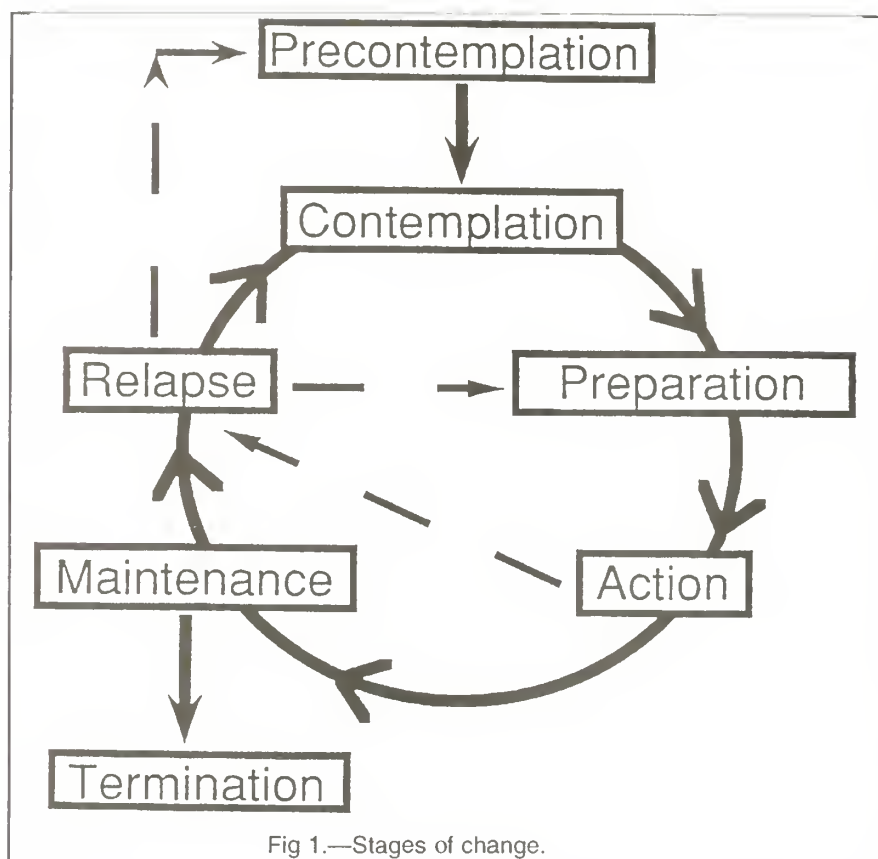


Fig 1.—Stages of change.

defined as the stage reached 6 months after quitting, is characterized by continued use of processes to help individuals to change or modify their experience to prevent slips or relapse.

An important finding by Prochaska and colleagues was that individuals frequently take several years to move through the processes of change before finally reaching a stable period of maintenance.³⁸ Moreover, individuals take an average of three or four cycles through the stages before finally becoming cigarette free.³⁸

How can this model help physicians to be more effective? By recognizing that the vast majority of smokers who visit a physician's office aren't ready to take action, physicians can modify their own expectations, back off on trying to get all of their patients to quit smoking, and develop strategies to attain intermediate outcomes, such as moving a precontemplator to the contemplation stage.^{6,38} Physicians using this approach are less likely to become frustrated and hopeless when the majority of their patients are unable to give up smoking in the short term. Additionally, matching intervention strategies to the stage of change actually enhances movement through the stages,³⁹ which, in the long term, may shorten the time it takes to reach stable maintenance.

Matching Interventions to the Patient's Stage of Change

Patients in the precontemplation stage will respond best to motivational interventions that help them to begin thinking about quitting smoking.⁴⁰ Personalized information and feedback may help raise the smoker's awareness of the ways in which smoking is affecting their health. Personalized messages are more likely to be effective than mini-lectures. Asking the patients to reflect upon their feelings about smoking is another useful intervention.^{6,38} If feelings of demoralization are uncovered, they can be addressed by informing the patient that even the most committed smokers may make several

quit attempts before they are successful.

Contemplators may also express negative feelings or fears about quitting. Clarification and legitimization of their feelings and expressions of support and respect may help these patients to feel heard and understood.⁶ Statements such as, "I'm glad that you're thinking about quitting" are especially useful since they reinforce the patient's interest in quitting. Even if they do not decide to quit in the near future, these interventions may help patients to feel more comfortable when talking to their physicians about smoking and also more receptive to future interventions.

It is also useful to explore contemplators' reasons for smoking as well as other barriers to quitting so that potential solutions for overcoming barriers can be discussed.^{6,38} For example, if a patient reports that she depends on smoking to help her to manage her weight, the offer and provision of alternative weight management strategies may tip the balance toward a decision to quit smoking. If a smoking patient's spouse or other family member also smokes, an offer to help both of them to quit may remove another barrier. Contemplators who become chronically stuck in this stage may benefit from encouragement to take small steps toward action, such as cutting down the number of cigarettes they smoke, delaying their first cigarette of the day, or trying to quit for just 24 hours.^{6,38}

When the patient is finally in the preparation stage or ready for action, appropriate action-oriented strategies can be advised or prescribed. Several other reviews as well as articles in this issue have described strategies for patients in action or maintenance stages in considerable detail.^{9,41-44} Useful interventions for patients in action (Table 3) include: setting a specific quit date with the patient, writing a contract, providing self-help materials, prescribing nicotine replace-

Table 5- Sources of Self-Help Materials and Other Materials for Patients

American Cancer Society (800) 227 2345 722-8480	Smart Move The 50 Most Often Asked Questions About Smoking and Health and the Answers
American Heart Association (214) 822 9380 728-5300	Calling it Quits
American Lung Association (212) 315 8700 421-6487	Freedom from Smoking for You and Your Family A Healthy Beginning: The Smoke-Free Guide for New Parents
National Cancer Institute (800) 4 CANCEER	Clearing the Air Why Do You Smoke?

ment (when appropriate), teaching behavioral skills (eg, self-monitoring, goal setting, self-reward, stimulus control, substituting alternative behaviors, relaxation exercises, coping skills training), referral to formal treatment programs, and enhancing social support. Individuals are most successful when multiple cognitive and behavioral strategies are used.^{38,42,44}

Pharmacologic agents are effective as interventions for smoking cessation when used in conjunction with behavioral interventions.¹⁴⁻¹⁶ Among the agents used to treat nicotine dependence, nicotine transdermal patches are relatively safe and easy to use and have been found to be modestly effective when combined with limited adjuvant behavioral counseling in general medical settings.^{17,18} One-year abstinence rates of 17% and 11% have been achieved in two European studies performed in the primary care setting.^{17,18} Research has also indicated that their efficacy can be enhanced when additional behavioral treatment is provided.¹⁴ Guidelines for the use of the nicotine transdermal patch are listed in Table 4. Excellent review articles on the use of nicotine transdermal patches and other agents are available.^{14,15,44}

Encouraging patients to begin or continue a program of regular exercise is another useful intervention for patients in action or maintenance. Exercise can serve as both a coping strategy and a mechanism to avoid or manage weight gain associated with quitting.⁴⁵

When physicians and office staff are not able or willing to spend the time necessary to teach behavioral skills to patients, motivated smokers can use effective self-help materials (provided by government or voluntary agencies and pharmaceutical companies) (Table 5).

Primary care physicians are in the unique position of having multiple opportunities to intervene with smokers over a period of years. Therefore, the physician and office staff can repeatedly assess the results of interventions and adjust the intervention strategy to meet the patient's needs as they emerge. Follow-up visits become especially important when the patient is in action or maintenance stages. Since the vast majority of patients will relapse after attempted abstinence, follow-up visits can be used to help the patient use relapse as an opportunity for learning. By exploring the circumstances that led to a return to smoking, the physician and patient can develop a revised plan that includes specific strategies to address the "triggers" that

Table 6.—A Patient-Centered Approach to Smoking Cessation: 5 As^{6,34,47,48}

Address the agenda

- Express desire to talk about smoking
"I'd like to talk to you about smoking"

Assess

- Stage of change¹
"Are you intending to quit smoking in the next 6 months?" If yes, "Are you intending to quit smoking in the next month?" If yes, "Did you try to quit smoking in the past year?"
- Level of nicotine dependence
- History of smoking related symptoms and illness
- History of previous quit attempts or withdrawal symptoms
- Knowledge of health risks of smoking
*"What do you **know** about the risks of your continued smoking?"*
- Reasons for wanting to quit smoking
- Reasons for wanting to continue to smoke
- Feelings and concerns about quitting
*"How do you **feel** about giving up smoking?"*
- History of psychiatric comorbidity

Advise:

- Provide information
- Correct misunderstandings
- Personalize risk: relate to patient's medical and family history
- Personalize benefits of quitting
- Tell patient that you would like him or her to stop smoking

Assist:

For all patients (especially precontemplators and contemplators):

- Provide support: state willingness to help
"I'd like to help you with your smoking problem"
- State understandability of patient's feelings
"I know it's hard to quit smoking"
- State respect for patient's previous efforts, provide reinforcement
"I am pleased that you tried to quit before"
- Express optimism about chances for success
- Identify barriers and solve problems
- Identify potential supports and resources

For patients ready to quit:

- Describe options available for quitting
- Negotiate selection among options
- Set quit day
- Provide resources, materials
- Prescribe nicotine replacement (when appropriate)
- Teach behavioral skills
- Refer, when appropriate

Arrange follow-up:

- Schedule follow-up appointment or phone call (whether or not the patient decided to quit)

At follow-up, if the patient attempted to quit, review results

If not abstinent:

- Analyze what went right and wrong
- Attempt to solve problems, overcome barriers
- Reinforce effort
- Encourage repeated attempts
- Consider more intensive treatment or referral
- Arrange further follow-up

If abstinent:

- Analyze what went right
- Identify potential problems and solutions
- Reinforce effort
- Arrange further follow-up

¹ A no answer to the 1st question = precontemplator

A yes answer to the 1st question + no answer to 2nd = contemplator

A yes answer to all three questions = preparation

led to relapse. One may also learn that the patient experienced the development or exacerbation of an underlying psychiatric disorder, since there is an increased risk of alcohol and other substance use

disorders, depressive disorders and anxiety disorders in smokers compared to nonsmokers.^{43,46} These disorders may require specific treatment or referral before the patient is able to quit smoking.

The 5 As: a Stage-matched Patient-centered Strategy

Lack of counseling skills, perceived ineffectiveness and lack of confidence are important barriers to counseling about smoking in the primary care setting. Recent research has demonstrated that physicians can be taught to use patient-centered counseling skills and, after training, perceive themselves as having significantly more influence on their patients who smoke.³⁴ Moreover, research has also demonstrated that smoking cessation rates are significantly increased when physicians use a patient-centered counseling approach in primary care settings.¹⁰

The stage-matched approach to smoking intervention described above has been integrated with a patient-centered model for patient education and counseling developed in parallel by Ockene and colleagues³⁴ and Grueninger and colleagues.⁴⁷ The result is a series of questions and statements, outlined in Table 6, called "The 5 A's", which is also adapted from the National Cancer Institute's physician-delivered smoking intervention program.⁴⁸

The 5 As provide the physician or office staff with a detailed list of specific tasks, questions and statements that may be utilized in the counseling intervention. During an individual session with a patient, only some of these items will be addressed, depending on time constraints and the interest of the patient and provider. However, the 5 primary steps: Address the agenda, Assess, Advise, Assist and Arrange follow-up, may be used with every patient during any visit. The strategy can be used effectively in as little as 3 minutes, though one may choose to extend the counseling session as long as a half-hour.

The first step, or first "A" is to "Address the agenda," by bringing up the issue of smoking. Identification of the patient's stage of change is a central aspect of the next "A", "Assess". The results of this assessment will determine the focus of the physician's subsequent efforts. Assessment of the patient's smoking history, including the level of nicotine dependence and prior quitting history are also essential components of this step. "Advise" is the third "A," providing personalized information to deliver a strong motivational message. "Assist," the fourth "A" is the step that provides stage-matched interventions. Assist is subdivided into two categories, one primarily for those who are in an early

stages of change, and another for those who are ready to quit. The final "A" is "Arrange follow-up," an essential component of the counseling strategy.

The process of the 5 A counseling intervention is called "patient-centered" because it is stage-matched, it stresses assessment and "asking" rather than "telling," and active involvement of the patient is solicited in the negotiation and selection of treatment options. Also, special emphasis is placed on using interventions that build a positive therapeutic relationship, such as empathy, legitimization and respect. The use of empathy has been shown to be especially effective in motivating precontemplators and contemplators to move toward later stages of change.⁴⁰

Organizational Systems to Support Office-Based Smoking Interventions

Barriers to the provision of smoking counseling in primary care include lack of organizational support and limited availability of materials to aid physicians and patients in smoking cessation efforts. Kottke, Solberg and Brekke have described the organizational components and systems that are essential to the delivery of effective and consistent counseling in primary care office settings.⁴⁹ An amended list of these components is presented in Table 2.

Because research has demonstrated that physician-delivered smoking cessation interventions are most likely to be effective when physicians are routinely reminded to intervene with all smoking patients by chart stickers or similar reminder systems,^{8,50,51} these systems should be integrated into all office practices. The reminders do not need to be elaborate—a simple cigarette sticker on the chart will do—but they need to be used routinely by all office staff to work. Recently, Fiore suggested the use of a vital sign stamp that includes smoking status along with blood pressure, pulse and temperature as a device to remind staff to assess and intervene with smokers.⁵² His article contains a figure that can easily be copied and made into a working stamp. The routine use of smoking history questionnaires can also serve as a reminder as well as save time.

Clearly, training of physicians and office staff is essential for the development of effective counseling skills. Training in basic counseling techniques can be accomplished in 2 to 3 hours.^{24,26,34,35,53} However, several of these studies used

residents as subjects. Many physicians, especially those who are less motivated to provide counseling interventions to their patients, are less likely to attend continuing medical education sessions that last more than 1 hour. Innovative strategies to provide physicians with training in counseling skills, such as the use of academic detailing,⁵⁴ are needed to help disseminate these skills to the majority of physicians in community-based settings. The use of trained nurses and other office staff as smoking counselors is effective and minimizes demands on physicians.¹² Training and orientation is also helpful for staff regarding the use of assessment instruments, reminders, patient resources and follow-up systems.

Resources for patients, physicians and office staff are important tools that enhance the capacity of the health care provider to provide information and advice. Self-help manuals for smoking cessation are effective⁴⁴ and are available through voluntary agencies. Though most of these materials have been developed for smokers in preparation or action stages, materials such as the National Cancer Institute's "Why Do You Smoke?" pamphlet are geared toward precontemplators or contemplators. The pharmaceutical companies that produce nicotine transdermal patches also have developed useful self-help materials that are available from their field representatives.

An excellent manual for physicians is published by the National Cancer Institute (NCI).⁴⁸ The manual provides practical and proven guidelines for individualized patient counseling as well as for developing office procedures and systems to support smoking interventions. Appendices contain lists of resources and assessment and tracking forms that can be copied for office use. The manual can be ordered by calling the Cancer Information Service, 1-800-4-CANCER. An office kit is also available that contains chart stickers, office posters, patient stop smoking contracts and the NCI self-help guide. The American Academy of Family Physicians has developed a similar kit, available by calling 1-800-274-2237.

Another important resource is a list of local smoking cessation programs that can be used to refer patients who express an interest in more formal or intensive treatment. Our NCI-funded project, Counseling Smokers, has created a referral list which is available from the RI Department of Health or directly from us (331-8500, ext 3731).

Once an office has decided to imple-

ment a system for supporting smoking interventions, the establishment of a specific policy that is endorsed by all staff is a useful device for generating staff commitment and delineating specific roles among staff. For example, a policy might identify who is responsible for such tasks as insuring that patients complete smoking questionnaires, ordering patient materials, or providing follow-up calls or letters. Identifying a single office staff person to be responsible for coordinating all smoking intervention activities is useful in larger offices or clinics. A policy to establish a smoke-free office is another useful step that clearly demonstrates a commitment to reducing the health risks of all patients, visitors and staff. The presence of posters and prominent displays of patient education materials also makes a "statement" that smoking cessation is a priority of the office's physicians and office staff.

Finally, Kottke and colleagues have stressed the importance of developing a "maintenance" program once an office has implemented several systems for supporting smoking intervention efforts. A maintenance program may include regular audits of charts to provide feedback to staff, spirit-building activities (eg, parties for achieving modest goals), and repeat training sessions to retain and enhance skills.

Kottke, Solberg and colleagues have recently demonstrated the feasibility, acceptability and effectiveness of a comprehensive system to support smoking cessation programs in primary care clinic settings.^{55,56} These investigators recently tested a strategy to disseminate office systems and staff training within a population of primary care clinic sites in Minnesota. Though adoption of the system was generally incomplete among the intervention sites, the intervention significantly increased the rates at which the intervention clinics identified their patients who smoked, advised them to quit smoking, and commended those who had recently quit smoking.⁵⁵

Physicians Counseling Smokers, funded by NCI, is currently testing a strategy for disseminating smoking cessation interventions among more than 250 Rhode Island primary care physicians. Our intervention is multifactorial and includes the use of office practice consultants, or academic detailers, to meet with physicians and office staff in their office setting. Office practice consultants assist physicians and staff to choose smoking intervention materials and resources which best meet the needs of their prac-

tices. On-site and off-site training in the use of materials and counseling skills is also available. The staff of Physicians Counseling Smokers greatly appreciates the participation of Rhode Island physicians and office staff in the project. We hope we will be able to demonstrate the effectiveness of our dissemination strategy and thus generate new insights into how to best overcome barriers to the provision of smoking interventions by primary care physicians.

A barrier that has not been adequately addressed thus far is the lack of adequate reimbursement for smoking cessation counseling or nicotine replacement therapy. As others have pointed out, without reimbursement from third-party payers, it is unlikely that any primary care-based smoking intervention program will persist and thrive.⁵⁵

Conclusion

Primary care physicians and office staff can play a central role in reducing the morbidity and mortality associated with cigarette smoking. Physicians and office staff have multiple opportunities to intervene with smokers over time and research has demonstrated that physician-delivered smoking interventions are effective. However, studies indicate that physicians are not nearly as active in providing smoking cessation interventions as they might be. Deficits in primary care physicians' knowledge, skills and attitudes about smoking cessation interventions interact with systems and organizational barriers to limit the use of smoking cessation interventions in primary care.

We have described several strategies to help primary care physicians and their office staff overcome these barriers to provide effective interventions to their smoking patients. Use of the Transtheoretical Model of Change helps clinicians to characterize patients' intentions and behavior so that interventions can be matched to the patient's stage of change. A stage-matched approach is not only more likely to be effective, it is less likely to lead to frustration among physicians and office staff. The use of a patient-centered counseling strategy enhances clinician's confidence and effectiveness and facilitates patient participation in the behavior change process. This strategy is easily learned and inherently pleasing to most clinicians. Finally, the development of organizational systems to support smoking cessation interventions in primary care practice is feasible and effective, but much remains to be learned

regarding how to best disseminate these systems.

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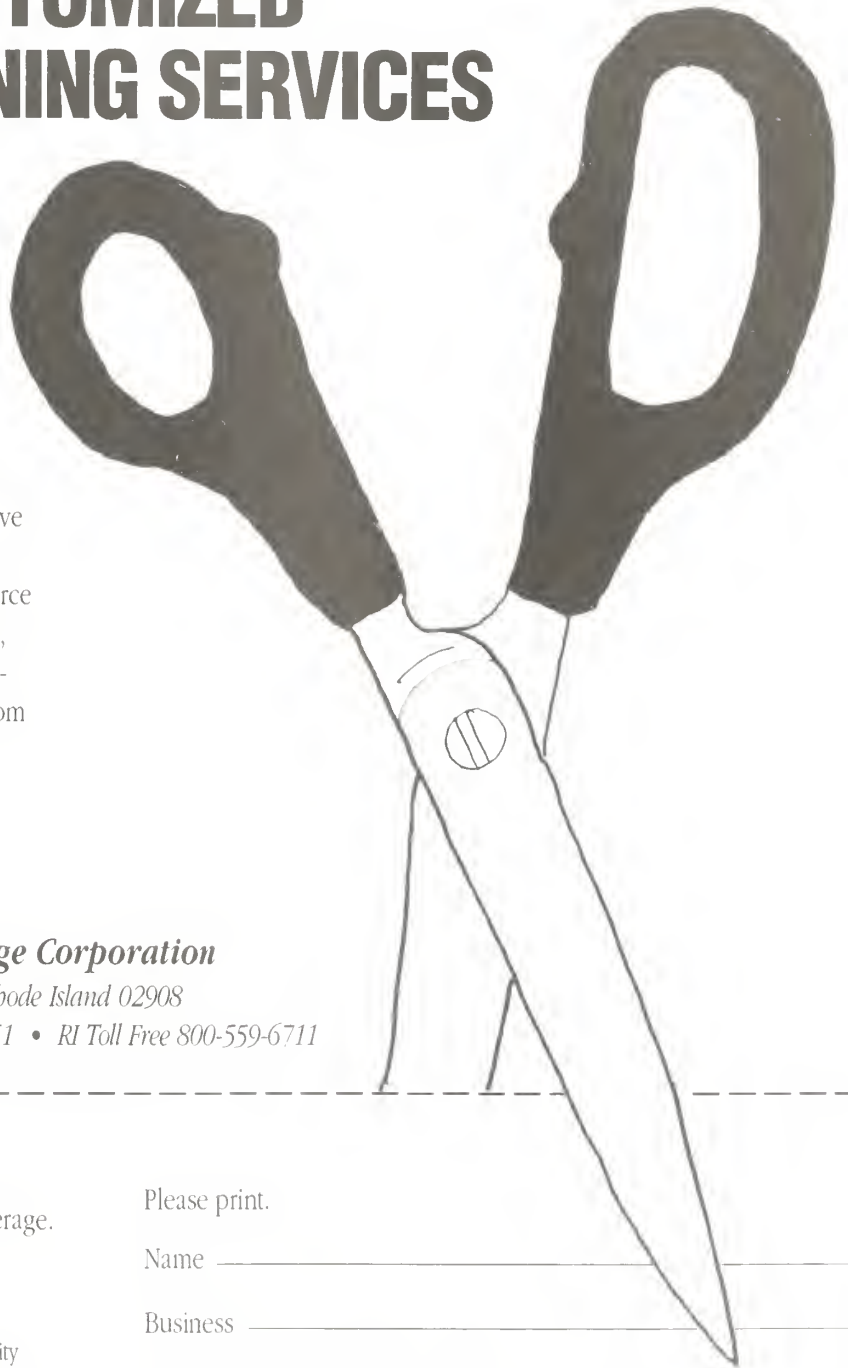
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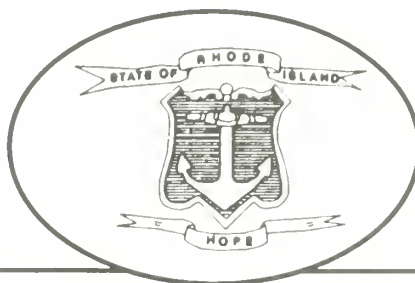
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HEALTH BY NUMBERS



Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Cigarette Smoking-Attributable Mortality, Rhode Island, 1989

Cigarette smoking is the single most preventable cause of premature death in the US and is responsible for more than 1 of every 6 deaths.¹ While total and per capita cigarette consumption have declined steadily since 1968, decreasing the number of cigarette smokers in the US and preventing the initiation of smoking among young people remain major public health challenges. Accordingly, they have been identified as national priority health objectives for the Year 2000 and have been proposed by the Governor's Task Force for Year 2000 Health Objectives for Rhode Island:²

Objective 3.4: "Reduce cigarette smoking to a prevalence of no more than 15% among people aged 20 and older."¹

Objective 3.5 "Reduce the initiation of cigarette smoking by children and youth so that no more than 15% have become regular cigarette smokers by age 20."¹

In 1989, cigarette smoking-attributable deaths accounted for 1859 (19%) of the 9550 deaths of Rhode Island residents and for 21% of deaths occurring among adults 35 and older. About twice as many smoking-attributable deaths occurred among adult males as among females (28% vs 14%). In 1989 11,659 years of

potential life lost (YPLL) before age 65 were attributed to smoking in RI.

The estimates of cigarette smoking's impact on mortality and YPLL in RI for 1989 were based on calculations performed on 1989 Rhode Island resident death data using the Smoking-Attributable Mortality, Morbidity, and Economic Cost (SAMMEC)³ software developed by the Centers for Disease Control and Prevention (CDC). SAMMEC uses attributable risk formulas to estimate the number of deaths from neoplastic, cardiovascular, respiratory, and perinatal diseases associated with cigarette smoking (including environmental tobacco smoke). Rhode Island estimates for adults ages 35 and older and for infants under age 1 were based on 1989 mortality data and on the 1989 smoking prevalence data obtained from the Behavioral Risk Factor Surveillance System. The YPLL were calculated using standard methodology.³

All but a fraction of smoking-attributable deaths in adults result from three major categories of disease—cardiovascular, neoplastic, and respiratory. In 1989, 44% of the smoking-attributable mortality (SAM) in Rhode Island resulted from cardiovascular diseases; 37% from neo-

plasms; and 18% from respiratory diseases. Within these categories lung cancer, ischemic heart disease, and chronic airway obstruction combined were responsible for 67% of all SAM (Figure 1). While less than 1% of all smoking-attributable deaths were among infants, recent research indicates that 10% of infant deaths may be attributable to smoking.⁴

The prevalence of cigarette smoking has declined among RI adults, from 29% in 1985 to 22% in 1992 (Figure 2). However, the Department of Health's Adolescent Substance Abuse Survey for 1991 estimated that 17% of children attending grades 7 through 12 were smokers, with prevalence ranging from 8% of 7th graders to 29% of 12th graders. The survey also indicates that the majority of smokers among respondents to the survey began smoking before 9th grade.

Decreasing smoking-attributable mortality in Rhode Island requires a vigorous effort to maintain the decline in adult smoking, to protect non-smokers from environmental tobacco smoke, and perhaps most important, to prevent the initiation of smoking among adolescents.

The Department of Health is working
(Continued on Page 525)

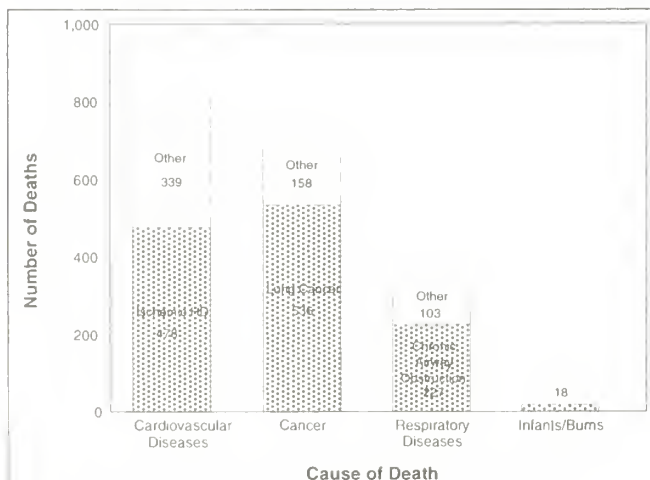


Fig 1.—Cigarette smoking-attributable deaths, by cause of death, Rhode Island, 1989

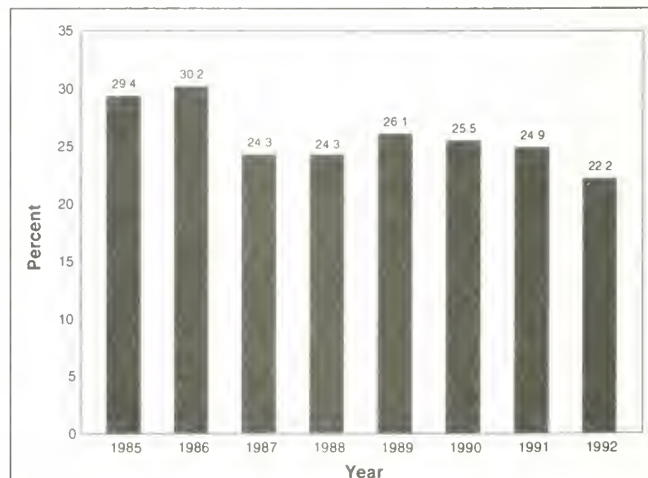


Fig 2.—Current cigarette smoking prevalence, ages 18 and older, Rhode Island, 1985-1992.

Submitted by Jana E. Hesser, PhD, Office of Health Statistics, RI Department of Health. Health by Numbers is edited by Jay S. Buechner, PhD, and William J. Waters, Jr., PhD.

IMAGES AND PATTERNS IN MEDICINE

Edited by Edward Feller, MD

A 71-year-old male resident of a nursing home was sent to the hospital following 8 hours of cramping pain in the lower abdomen. He had a lengthy history of constipation. A plain X-ray of the abdomen was obtained (see illustration below). Radiographic interpretation and commentary may be found on Page 528 of this issue of RHODE ISLAND MEDICINE.

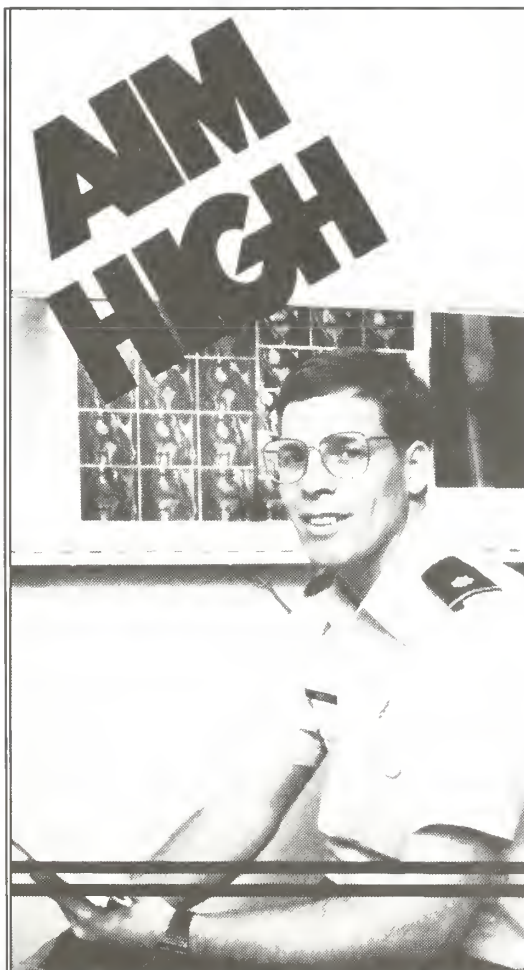
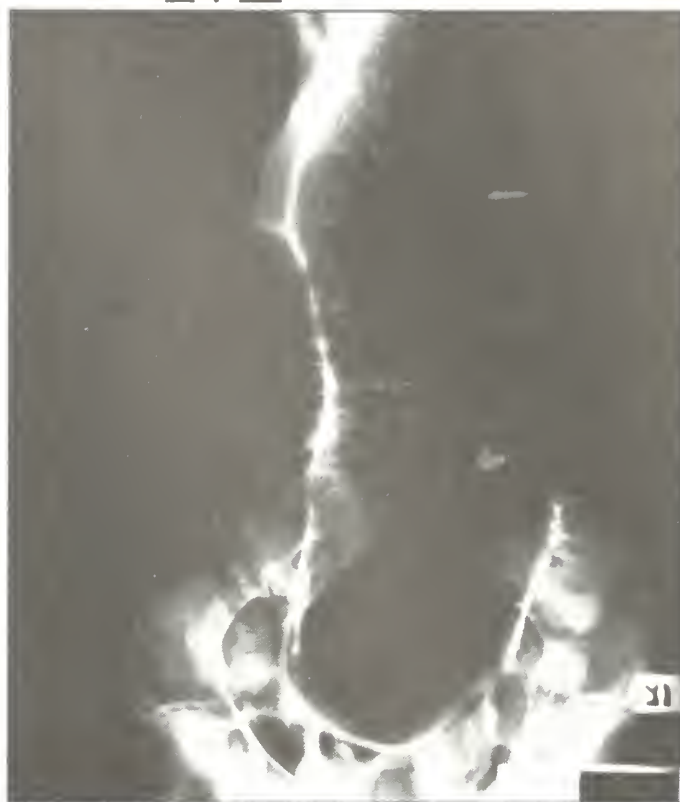
Health by Numbers

(Continued from Page 524)

collaboratively with community representatives and agencies towards these objectives through the activities of Project ASSIST and the National Cancer Institute-supported Youth-Oriented Tobacco Prevention and Cessation Project.

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

90 Years Ago (October 1903)

The lead article by John W. Keefe, MD, discusses catheterization of the ureters. Given the many technical improvements in urologic instrumentation, the author states that the cystoscope and ureteral catheters should be used more often both for diagnostic and therapeutic purposes. Specifically, he suggests that, "the general practitioner may, with a little perseverance so familiarize himself with their use and the appearance of the inside of the bladder, that a number of diseases now treated symptomatically, will be definitely diagnosed and consequently treated more rationally. Although the general practitioner may never become a highly trained expert he may acquire sufficient dexterity in the use of the cystoscope to materially aid him in his work." With various procedures, for example, the urine from either kidney may be obtained. Thus, the source of pus or blood may be identified and pyelitis may readily be distinguished from cystitis. The author then describes the sequence of steps needed in catheterizing the ureter. Removal of ureteral stones is described. The presence of impacted stones in the renal pelvis may be inferred by noting scratch-marks on the wax covering the tip of the ureteral catheter. The urine from a tuberculous kidney may show the pathognomonic organisms. The author urges the reader to inject urine into guinea pigs, in cases where tuberculous infection is suspected. Finally, the author lists the 75 cases in which he has undertaken catheterization of the ureters. While there may be negligible bleeding after the procedure, he observes, in each instance it cleared within 10 days.

H.G. Partridge, MD, describes a case of submucous fibroid complicating labor

and the puerperium, with retained placenta. Following the delivery, a large submucous neoplasm was identified. A marked, local streptococcal infection then developed, the tumor gradually sloughed away, and the patient made a good recovery. A second case of a ruptured uterus is also reviewed. The patient was a 32-year-old woman, pregnant for the seventh time. Labor was extremely difficult, made more so by a bony sacral projection. Version was used and a dead child was delivered. A short time later the mother died. A large rent in the uterus was noted.

50 Years Ago (October 1943)

The first article, by Charles C. Lund, MD, discusses burns. The author notes that recent military experience, particularly in the British Army, has reordered emergency techniques used in the treatment of burns. Thus, the routine use of escharotic agents (eg, tannic acid, picric acid, triple dye) may actually impede rather than advance healing and is now replaced by a simple bland ointment (eg, petrolatum or boric acid ointment). The writer then describes the definitive treatment for minor burns (ie, less than 5% involvement of skin surface), which includes pressure dressings (which should not be removed until healing takes place) and measures to prevent or eliminate secondary infections. The discussion then centers on major burns, the role of shock, the early and late complications of burns, the element of infection and its treatment, and finally the role of skin grafting.

Kalie K. Gregory, MD, (Assistant Superintendent of the Charles V. Chapin Hospital, Providence) writes a paper on acute anterior poliomyelitis, with particular reference to the 1943 epidemic in

Rhode Island. He cites the institutional experience with 83 cases, 69 of whom are still hospitalized. During this past 35-week interval, he notes, there were 5887 cases in the United States. In the prior year, there were only 1902 cases during a comparable interval. The author then explains the complicated and labor-intensive Sister Kenny treatment.

The Rhode Island Medical Society Committee on Maternal Mortality presents a 10-year study of maternal mortality in Rhode Island. The maternal mortality rate in 1932 was 5.7 per 1000 live births. In 1942, the rate was 1.9. Three categories of deaths are counted: Class 1, where the cause of death was non-obstetrical and pregnancy was only coincidental (eg, cerebral hemorrhage); Class 2, where the pregnancy was complicated by a pre-existing condition (eg, chronic heart disease); and Class 3, those deaths directly associated with pregnancy (eg, placenta praevia).

Editorials include an admonition to those physicians who have not yet sought a military commission to do so before they are drafted by the Selective Service System. Another editorial discusses tuberculosis in Providence, noting that there is a gradual reduction in annual mortalities from 127 in 1934 to a projected 104 in 1942. Another editorial advises the readers about what Christmas presents to send overseas to those in service. Do not send cigarettes, the editorial recommends, since the overseas military allowance for cigarettes is 10 packs per week per person. Instead, one may wish to send such utilitarian items as a good fountain pen, canned peanuts—or a good cigarette lighter.

This issue of the *Journal* carries a report from India, site of the 48th Station Hospital, written by MAJ Frank B. Cutts, MC. The report comments on living con-

ditions in India, transportation through the countryside, and the nature of the encountered medical problems. There is also a regular column on civilian defense measures.

25 Years Ago (October 1968)

Walter C. Cotter, MD, writes on use of tegretol in the treatment of tic douloureux. A total of 63 cases were treated and about 60% noted relief of pain without any adverse symptoms, although there were some transitory skin rashes, dizziness and nausea.

Sharad Y. Deshpande, MD, and Frank B. Cuffs, MD, discuss the causes of prolonged Q-T intervals in the electrocardiogram, based upon 30 patients with autopsy examination. The authors state: "The major cause of Q-T prolongation was hypocalcemia (at least 13 out of 30 cases)." Other causes included acute pancreatitis, hypoparathyroidism, quinidine and Pronestyl therapy, subarachnoid hemorrhage, and rheumatic myocarditis.

Charles Millard, MD, discusses the pulmonary manifestations in rheumatoid disease. The author concludes: "Although the major pathology and clinical evidence of rheumatoid disease is usually articular, it must be remembered that this is a systemic disorder. The connective tissues in any part of the body can be and often are involved. The lungs contain an abundance of connective tissue in the interstitial stroma and the extensive vascular system. An increasing awareness of this fact has led to more frequent recognition by the physician of rheumatoid lung disease in recent years."

Howard S. Browne, MD, discusses ischemic necrosis of muscle (acute anterior compartment syndrome) following repair of anterior compartment hernias, illustrating this with two personally observed cases.

Sharad Y. Deshpande, MD, Frank Merlino, MD, and Frank B. Cutts, MD, present two cases of ventricular tachycardia and fibrillation due to carotid sinus stimulation.

An editorial on smoking concludes with the following statement: "It is, therefore, incumbent on the medical profession to do all it can, individually and collectively, by precept and example, to aid the public in overcoming this definite cause of invalidism and death."

IMAGES AND PATTERNS IN MEDICINE

Interpretation and Comment (cf Page 525)

Sigmoid Volvulus

Volvulus, or twisting of a segment of the colon and its mesentery, is a relatively rare cause of intestinal obstruction. Sigmoid volvulus, the most common form, is frequently preceded by chronic constipation in an elderly patient. A characteristic complaint is inability to pass feces or flatus associated with crampy abdominal pain.

Plain abdominal x-rays demonstrate markedly dilated loops of large bowel. Pointing toward the obstruction is the so-called "bird's beak," a narrowing of the

air-filled colon. If peritonitis is present, resection of infarcted bowel is indicated. Endoscopic detorsion of the volvulus is the preferred treatment in the absence of ischemia. A flexible endoscope is introduced rectally and passed to the point of torsion. Then, a soft rubber tube is passed through the instrument beyond the point of torsion. This maneuver commonly produces immediate, and at times, dramatic expulsion of gas and stool. Detorsion subsequently occurs. In other cases, the obstruction may reduce spontaneously, though recurrence is common after both spontaneous or non-operative reduction. —Edward Feller, MD



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Specifications: Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins, using 8" x 11" non-erasable bond. Tables, charts, and legends should be submitted separately from the text and referred to by number (eg, Fig. 1 or Table 2, etc.) Number pages consecutively.

To expedite production and ensure accuracy, authors are **strongly encouraged** to submit articles as well as computer-generated tables and figures on floppy diskette, formatted in any major MS-DOS or Windows word processor (eg, Microsoft Word, Wordperfect, Wordstar, Xywrite, Multimate, etc.) Macintosh disks will be accepted provided text is saved in an ASCII file. If possible, Macintosh disks should be saved in DOS format, using Apple File Exchange. Diskettes must be accompanied with at least one printed copy of the manuscript. Diskettes will be returned upon request.

Title page: The first page of the manuscript should contain: (1) title of the contribution; (2) authors' name(s), highest academic degree, and institution; (3) address and phone number for communications; (4) a brief biographical description of each author, including specialty, practice location, academic appointment and hospital affiliation.

Abbreviations: Avoid the use of jargon and unnecessary abbreviations. Abbreviations used, especially of laboratory and diagnostic procedures, must be identified fully in the text within parentheses. The author(s) shall provide *Rhode Island Medicine* with a complete alphabetic list of such abbreviations with an explanation for each, on a separate page.

References: References shall be limited to those that are absolutely essential to the understanding of the article and should number no more than 20. The editor reserves the right to reduce the number when necessary. The author is responsible for the accuracy and completeness of the references. References should be compiled at the end of the article according to the order of citation in the text. In the text, they should be given as numerical superscripts. They should be typewritten, double-spaced under the heading "References." A complete journal reference includes: (1) authors' surnames and initials; (2) title of article and subtitle, if any; (3) abbreviated name of journal (abbreviations must conform to those used in the *Index Medicus*); (4) year; (5) volume number; (6) part or supplement number, when pertinent, and issue month or number when pagination is not consecutive throughout a volume; and (7) inclusive page numbers. A complete book reference includes (1) authors' surnames and initials; (2) surname and initials of editor or translator, or both, if any; (3) title of book and subtitle, if any; (4) number of editions after the first; (5) place of publication; (6) name of publisher; (7) year of publication; (8) volume number, if more than one; and (9) page numbers, if specific pages are cited. References should conform to the punctuation

and style set forth in the American Medical Association's *Manual of Style*, 8th ed.:

Journal Article:

1. Feinfeld DA, al-Achkar G, Lipner HI, Chirayil SJ, Hakim J, Avram MM. Syndrome of inappropriate secretion of antidiuretic hormone: Association with cavernous sinus thrombosis. *JAMA*. 1978;240:856-857.

Books:

2. Hollingworth JW. *Local and Systemic Complications of Rheumatoid Arthritis*. Philadelphia, Pa: Saunders; 1968.

Book Chapter

3. Epstein WL. Erythema nodosum. In: Samter M, ed. *Immunological Diseases*, 2nd ed. Boston, Mass.: Little, Brown; 1971;2:944-951.

Illustrations - Drawings and charts must be submitted in black ink on white paper. Laser printed graphs are acceptable provided they are printed at 300 DPI resolution. Photographs must be in black and white, submitted on 5 x 7 glossy paper. Illustrations must be numbered consecutively and their positions indicated in the text. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends should be submitted in a single list with the numbers corresponding to those on the illustrations. Recognizable photographs of patients are to be appropriately masked and must carry with them written permission for publication. Special arrangements must be made with the editors for excessive numbers of illustrations. Color plates are not acceptable.

Identification of Patients - Names and initials should not be used. When discussing individual patients use numbers (ie, Patient 1, Patient 2, etc.).

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Correspondence - Letters-to-the-editor and all manuscripts should be addressed to Stanley M. Aronson, MD, Editor-in-Chief, Box G, Brown University, Providence, RI 02912. All other correspondence relating to the publication should be addressed to: John P. Sulima, Managing Editor, *Rhode Island Medicine*, 8 Potter Hill Road, Westerly, RI 02891.

Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose response study. *Clin Cardiol*. 1991;14:146-151.

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation: Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic, although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia: Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle.

Antipyrene: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect (see DOSAGE AND ADMINISTRATION: Concomitant Therapy).

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids (1 hour prior to PRAVACHOL [pravastatin sodium]), cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitals, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a >50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallenian degeneration of retinoganglionate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallenian like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg/day or in rabbits at doses of up to 50 mg/kg/day. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia; loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

THE PRAVACHOL® DIRECTION
IN LIPID MANAGEMENT

Effective lipid management doesn't have to be tough



- Improves key lipids — significant reduction in LDL-C¹
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food


PRAVACHOL®
pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate. Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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ORIGINAL DEPARTMENT.

Communications

ON CHOREA.

By GEORGE HUNTINGTON, M. D.,
Of Piquette, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Philadelphia, Ohio, February 12, 1872.

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the voluntary muscles. There is no loss of sense or of volition attending these contractions, as there is in epilepsy; the will is there, but its power to perform is deficient, the desired movements are after a manner performed, but there seems to exist some hidden power, something that is playing tricks, as it were, upon the will, and in a measure thwarting and perverting its designs; and after the will has ceased to exert its power in any given direction, taking things into its own hands, and keeping the poor victim in a continual flinger as long as he remains awake, generally, though not always, granting a respite during sleep. The disease commonly begins by slight twitchings in the muscles of the face, which gradually increase in violence and variety. The eyelids are kept winking, the brows are corrugated, and then elevated, the nose is screwed first to the one side and then to the other, and the mouth is drawn in various directions, giving the patient the most ludicrous appearance imaginable.

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palm upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the neck is turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the muscles of the lower extremities are not affected, and I believe they never are alone involved. In cases of death from chorea, all the muscles of the body seem to have been affected, and the time required for recovery and degree of success in treatment seem to depend greatly upon the amount of muscular involvement. BOWEN refers to two cases in which the muscles of respiration were affected.

The disease is generally confined to childhood, being most frequent between the ages of eight and fourteen years, and occurring oftener in girls than in boys. DUFOSSE and RUFZ refer to 429 cases; 130 occurring in boys and 299 in girls. WATSON mentions a collection of 1,029 cases, of whom 733 were females, giving a proportion of nearly 5 to 2. Dr. WATSON also remarks upon the disease being most frequent among children of dark complexion, while the two authorities just alluded to, DUFOSSE and RUFZ, give as their opinion that it is most frequent in children of light hair. In every case visiting the clinics

Movement Disorders

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Movement Disorders: Resources in Rhode Island

The neurological subspecialty of movement disorders has been a rapidly expanding field since the introduction of levodopa a quarter century ago. New illnesses such as progressive supranuclear palsy and cortico-basal ganglionic degeneration have been recognized. Disorders such as torticollis, writer's cramp and Gilles de la Tourette syndrome, previously believed to be psychogenic are now thought to have an organic etiology amenable to medications. New disorders such as post-anoxic myoclonus, tardive dyskinesia and the levodopa-induced phenomena in Parkinson's disease have been created. There are large enough numbers of patients that most academic medical centers in the US have been creating their own movement disorders unit. In Rhode Island alone, there are an estimated 2000 patients with Parkinson's disease.

It is a field rich in phenomenology, where the history and the physical examination are everything. Laboratory tests including imaging studies are usually of little value. And, although we know a great deal about these various disorders, answers to the basic problems remain elusive. The phenomenological complexity of this field lies somewhere between the simplicity of nerve and muscle disorders and the daunting complexity of behavioral, language and cognitive dysfunction. The disorders have taught us important lessons about normal brain biochemistry and are providing insights into various psychiatric problems and their chemical underpinnings as well.

The field is treatment oriented. It gives the lie to the belief that neurology is solely a diagnostic field of intellectual interest. The treatment of Parkinson's disease extends both quality and duration of life. Botulinum toxin has transformed

life for many with torticollis and other dystonias. Clozapine is the first step in the road to the treatment of psychosis without iatrogenic movement disorders. Yet much needs to be done. The gene for Huntington's disease has been identified but has not yet explained the disease. Tantalizing clues have been found that might point to the cause of Parkinson's disease. As basic research is pursued to solve these various puzzles, we strive to improve treatment for our current and future patients. This issue of Rhode Island Medicine describes the state of the art, 1993.

Not all patients need specialty care, for those who do, or for those who want to help advance the research that will provide better care, such help is available in Rhode Island. The authors of the enclosed articles all have special interest and experience in movement disorders and are also involved in clinical research. A list of such research projects can be obtained from the Brown University Parkinson's Disease and Movement Disorders Unit at the Roger Williams Medical Center. Special services are available as follows:

Brown University Parkinson's Disease and Movement Disorder Unit

456-2231

Dystonia Medical Research Foundation

One East Wacker Drive
Suite 2900

Chicago, IL 60601-2001
312-755-0198

Huntington's Disease Support Association

Attention: Tom Vescera
31 Oneida Street
Pawtucket, RI 02860
724-9622

International Tremor Foundation

360 West Superior Street
Chicago, IL 60610

National Spasmodic Torticollis Association

1-800-HURTFUL

Parkinson's Disease Referral and Information Center of Rhode Island

K. Cullen, RN, MA, Clinical Director
456-2456

Progressive Supranuclear Palsy: The Society for PSP

3737 Courthleigh Drive
Randallstown, MD 21133-4827

Tourette Foundation

212-224-2999

Tourette Syndrome Support Group of Rhode Island

Attention: Christine
789-6848

Joseph H. Friedman, MD
Chief, Division of Neurology
Roger Williams Hospital

Virus-speak

In May 1993, health departments in several southwestern states took note of a new, sometimes fatal, acute respiratory distress syndrome, which, according to their laboratory tests, was caused by an agent of the hantavirus group. Hantavirus? Who or what is Hanta? And why no customary spacing between "hanta" and "virus"?

If all the known species of virus, about 2000, were to have been discovered, analyzed and characterized in a single day, our scientific community willfully would have adopted a rational taxonomic schedule readily understood by all. They would have asserted that an orderly system of classification, based upon credible criteria, was a necessary prelude when confronting an allegedly new agent. And while they labored on all of this taxonomy, these scientists would certainly have looked back with admiration upon the systematic efforts of an 18th century Swedish physician-botanist—Carl Linnaeus—who had developed a

Latinized binomial nomenclature for the entire plant and animal kingdoms, a system now globally adopted. But Linnaeus had all his plants and animals spread out macroscopically before him; and he could leisurely categorize his specimens, giving no thought to such complexities as nucleic acid type, ultrastructural morphology, or the urgencies of human sickness. Moreover, he did not have to confront epidemics and outraged journalists demanding immediate identification of the putative pathogen. The media, to the older scientists, were merely fluids for culturing.

Viral realities, of course, have been consistently otherwise. The diseases caused by viruses came first, centuries before science even acknowledged the existence of filterable infectious agents. One by one, and only during the last century then, did each viral pathogen come to be isolated. At all levels of human activity, it seems, the crime is always more obvious than the criminal.

The street names given to diseases that we now know to be viral have been derived from an assortment of languages including Greek (eg, herpes), Latin (eg, rabies, variola), Germanic (eg, measles, pox, mumps), and Italian (eg, influenza, varicella). Once rooted in the vernacular, however, these traditional names were not to be easily displaced. Confusion abounded and each language had its own names for these diseases. The lack of a uniform language base, such as Latin, was matched by an absence of any consistent criteria in the choice of the name. Indeed, many chosen names represented utter irrelevancies or clinical features of marginal value; thus, for example, the name influenza was derived from an Italian word suggesting astrological influences upon the sickness; and measles arose from an older Germanic word meaning misery.

By the decade following World War II, the techniques for viral isolation, such as tissue culture, permitted the identification of large numbers of previously unknown viruses; and many were isolated from persons without obvious disease. The task was then turned upon itself to find diseases that matched these orphan viruses. The number of species-discrete viruses parasitizing vertebrates now total about 950, the great majority of which are already shown to cause clinical disease, under certain circumstances.

Numerous international congresses have been convened to arrive at a common taxonomy for the rapidly accumu-

lating species of virus. The rules agreed upon stress the following: The new nomenclature shall be international, whenever possible in Latin and shall apply to all viruses (ie, whether vertebrate, insect, bacterial, or plant). In contrast to the naming of bacteria, no person's name shall be used. Viral families shall end with —viridae (eg, *poxviridae*), and genera shall end with —virus (eg, *myxovirus*), with no spacing. Sigla, other than those already established, shall be avoided. Seven criteria defining the characteristics of each of the viral families, genera and species, shall be recognized: the type of nucleic acid (ie, DNA or RNA), whether single- or double-stranded, molecular weight of the nucleic acid, shape of the agent, shape of the nucleocapsid, host(s), and vector(s), if any.

Sigla are nonsense words, assembled for purposes of brevity, and typically using the initial letters of a longer phrase. Siglum (singular), comes from the Latin, *sigillum*, meaning a sign or symbol. Sigla in common discourse include such contrived words as Nabisco, Alcan, ALCOA, NATO, and Conrail. Among viruses, one encounters such sigla names as *Papovaviruses* (*papilloma*, *polyoma*, *vacuulating agent*), *Reoviruses* (*respiratory enteric orphan*), *Arboviruses* (*arthropod-borne viruses*) and *Picornaviruses* (*pico*, meaning very small (Spanish), plus RNA, the type of nucleic acid). Sigla are more common in plant virus nomenclature (eg, *Tobamo* virus, from *tobacco mosaic virus*).

The currently accepted names of the 17 families of vertebrate viruses are of either Greek or Latin origin. *Iridoviridae* are named after *Iris*, Greek goddess of rainbows (selected because of the iridescence of infected tissue). *Adenoviridae* are named for the Greek word meaning gland, since these viral agents were first isolated in lymph nodes. *Parvoviridae*, from the Greek, *parvus*, meaning small; *retroviridae*, from the Latin meaning backwards; *rhabdoviridae* from the Greek, *rhabdos*, meaning rod-shaped. (This family includes rabies, which was formerly called Lyssa virus, also from the Greek meaning rage.) *Togaviridae*, a large family including the insect-borne forms of encephalitis, as well as dengue and yellow fever, arises from the Latin, meaning cloak; *caliciviridae*, from the Latin, *calix*, meaning goblet, denoting the cup-shaped depressions on the viral capsule, as seen by electron microscopy; *arenaviridae*, from the Latin, *arenosus*, meaning sandy, from its electron-micro-

scopic appearance; *coronaviridae*, from the Latin, meaning crown, again based on the electron microscopic appearance of the viral capsule; and *Bunyaviridae* (including many of the hemorrhagic fevers) named after the village in Uganda, Bunyamwera, where this family of virus was first encountered.

Most species names of the *Togaviridae* and *Bunyaviridae* families are of geographic origin signifying the places where isolation was first effected. The older isolates still maintain the spacing between the name and the word, virus. The newer ones dispense with this. Thus, we have Semliki forest virus (Zaire), Ilheus virus (Brazil), Cocksackie virus (New York), Rift Valley Virus (east Africa) and—finally—Hantavirus (named after the Hantaan river, east Asia, where the virus causing Korean Hemorrhagic Fever was first recovered).

Organization is probably better than chaos, whether it be in managing nations or naming vagrant viruses—but not too much organization. The polar extremes, either anarchy or petrified commandments, can be dangerous. “The world,” observed Valery, “is equally threatened with two catastrophes: order and disorder.”

Stanley M. Aronson, MD

Four Simple Rules

While an undergraduate student at Barnard College, in 1982, Ms Angela DeVecchi developed a small scalp lesion that was histologically identified as extranodal Hodgkin's disease. She was treated with chemotherapy at Memorial Sloan Kettering Cancer Center. Two years later she had a relapse, with nodal involvement, again treated with chemotherapy. In 1990 another recurrence was treated with chemotherapy and bone marrow transplantation (Dana Farber Cancer Institute). Ms DeVecchi is an elementary school teacher, and in some of her spare time, a volunteer teacher to Brown University medical students. Based upon her experience as a patient during extended and multiple hospitalizations she has assembled four simple rules addressed to hospital physicians. Robert Hopkins, MD, of Brown's department of surgery, has urged that RHODE ISLAND MEDICINE share these rules with its readership. With Ms DeVecchi's permission, then, we list her four simple rules on the next page.

FOUR SIMPLE RULES

Or

How to Humanize a Dehumanizing Experience When a Person is in the Hospital

I. Consider yourself a guest in the patient's room

- "Knock" before you enter.
- Apologize if you must wake the person.
- Be sure to draw the dividers *fully* in a semi-private or exposed room.
- Introduce yourself and anyone with you.
 - Explain what role each person on the team has. The doctor parade can be very confusing.
- Address the person *by* last name unless you are asked otherwise.
- *Never* refer to the person as "the patient" in front of him or her.
- Sit down when you're chatting with the person.
 - Try not to stand over them. This can be intimidating.
- Don't move furniture or belongings around without putting them back where you found them.
- If you must turn any lights on, turn them off when you are through. The same goes for opening window curtains. Close them when *you* are through.

II. Be particularly sensitive when examining a person in bed

- Ask before you touch. Explain what you are doing and why.
- Warn the person if it might hurt and how.
- Warm your hands and your stethoscope!!
- Try to keep the person as covered as possible. It's colder for them than it is for you.

III. Listen (and learn)

- Always ask the person if he or she is comfortable.
 - He or she might not otherwise tell you.
- Encourage questions, no matter how trivial.
- Try to make time for loved ones to ask questions or share thoughts.
 - Their observations can be very helpful.
 - Encourage them to write down questions as they think of them. People often forget under pressure.

IV. Explain

- Knowledge is power. People in the hospital need as much as they can get.
- Use simple language, not medi-speak.
- Tell the person when you will be back.

Tracy's wrist-communicator, it nevertheless is reduced to the dimensions of a king-sized pack of cigarettes, an item incidentally rarely carried by today's physician.

Telephones and medical practice have been intimately involved with each other since the instrument was invented. In the early days there was a felicitous informality to telephonic communication. One opened the circuit by picking up the ear piece and when a pleasant female voice responded to your presence, you requested, in courteous words, to be connected with a Mr Galsworthy or a Miss Wharton. The number of operative phones, before 1878, was so small that the operator would have known which circuit you wished to be connected with. According to historian Richard Brodsky, the situation changed during the 1879 measles epidemic in Lowell, Massachusetts. A physician named Moses Parker, fearing that all five of the local telephone operators might simultaneously become ill and that their substitutes hence might not know the circuitry assignments, recommended that each customer be given a widely advertised number so that callers could then request connection, for example, to telephone number 47 rather than to a Mr Eliot. In the next decade, the number of new telephones increased so rapidly that this simple numbering system became inadequate and district names were added to the telephonic code number (eg, Cranston 1234). This evolved further into the 7-digit alphanumeric identification, easily accessed by the automatic dialing procedure, which in turn gave way to the current 10-digit area code system, and, for international calls, the 16-digit numbers. (Since the world population is about 6 billion, why do we need 16-digit phone numbers? Even if we assume that each man, woman and child has a personal phone, we would then need only a 10-digit number to provide each person with a singular numeric signature; the extra six digits are there to simplify the computer-managed circuiting of each call.)

The last 4 numbers of the numeric sequence are, of course, not randomly handed out. Customers receiving numerous calls (eg, hospitals, major companies, busy law firms) are provided with easy to remember numbers such as sequences ending with 3 zeros (eg, 6000), a repetition of the same number (eg, 1111), a palindromic number (eg, 2332), or (since our dials are still alphanumeric, carrying letters as well as digits) numbers that spell out meaningful words. A deli-

The New Professional Symbol

There was a time when the stethoscope was the private physician's preeminent piece of equipment; it served both as a diagnostic aid and as a visible symbol of the profession. The rubber tubes projecting from the coat pocket proclaimed physicianhood as readily as the shouldered ax defined the woodsman.

Times are changing and now the mobile cellular telephone, and the ever present beeper, are the necessary instrumental accompaniments of the active practitioner. Four decades ago, a telephone call might have reached physicians at their offices, at hospitals, or at home. In the years since, telephones have

proliferated and become available in hotel bathrooms, commercial aircraft, street corners and even Amtrak trains. But there still remained inevitable gaps in instant availability while the physician was driving, in a gymnasium or elsewhere. Lest these gaps in access be left unresolved, we now have the newer mobile communication technologies to give us wall-to-wall availability.

Whatever function engages today's physician, noble or ignoble, contact now can be virtually instantaneous. The strident beeper, harnessed to the belt like a life-sustaining instrument, cannot be readily ignored; and the portable cellular telephone can break through all manner of barriers, interrupting everything from innocent recreation to existential reverie. While not yet shrunken to the size of Dick

catessen, therefore, might request a 468-3647 number, since their customers merely have to remember the phrase HOT DOGS when dialing them. A pediatrician, in turn, might request that the phone company assign her the number 222-9362 (which spells out BABY DOC). Some caution, of course, has to be exercised. A surgeon not skilled in Scrabble might choose 437-6427, which spells HERNIAS, without realizing that it also spells HEROICS.

To what extent are Rhode Island physicians given imposing telephone numbers? A survey of the office telephone numbers assigned to physician members of the Providence Medical Association reveals that 34.7% have preferential numbers, that is, numbers more readily remembered than random sequences. The commonest of these is a 4-digit sequence ending in two zeros (eg, 6700) with about 1 of every 6 physicians possessing such a number. About 3% of physicians have palindromic numbers; and slightly more than 5% of physicians have repetitive 2-number combinations (eg, 2121 or 3366). The most memorable sequence in Rhode Island is the proud possession of a group of local ophthalmologists who, with clarity of vision, chose 2020.

A functioning phone, cellular or conventional, is a genuine comfort, offering its owner a tangible link with the world. Communication, to sapient creatures, is a vital human resource: each incoming call assures us that we are connected; and every connection allows us to discuss issues ranging from trivia to life's Great Questions. This sense of security can be fully appreciated only when phone service is disrupted. Encountering a dead phone is one of life's disquieting experiences. Worse than being deaf and mute, it means, in small measure, being ostracized.

Is there any downside to all of our telephonic extensions and services? Perhaps being inescapably part of an active telephone network corrupts our inner capacity to think independently. Once, an unlisted phone had been considered a status symbol. Now a life occasionally free of telephonic access, providing modest intervals of blessed stillness, might also become a mark of elitism. Being unconnected can sometimes have its charms. Furthermore, leaving questions unanswered for brief spells serves to remind us that many events evolve—with or without our pronouncements.

Stanley M. Aronson, MD

Letter to the Editor

'Listen to the Patient, Doctor'

To the Editor:

Dr Schiffman's report of his orange patient prompts my response: the case qualifies as exotic uniqueness which the editor dislikes, but there is educational value and support for the old admonition "Listen to the patient, Doctor. He's telling you the diagnosis."

Bertor: Roueché in *The Orange Man*

entertainingly details the hospitalization, the extensive and fruitless work up of a patient whose diagnosis was finally made by learning that he was continually eating carrots and drinking great quantities of tomato juice.

Frank Lepreau, MD
Fall River, Mass.

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Parkinson's Disease Update

Joseph H. Friedman, MD

... Parkinson's disease may be an example of an environmental toxin-causing disease in a predisposed person.

Parkinson's disease (PD) is the fourth most common neurological disorder of older Americans, after dementia, seizures and stroke. It affects about 1% of the Caucasian population above the age of 65 and an unknown but considerably smaller percentage of African-Americans.¹ Therefore, all physicians, aside from pediatricians, will see patients with this disorder.

The focus of research in PD has broadened considerably in recent years to include the study of the neuronal degenerative process. Recent advances in transplantation and neurophysiology are being exploited to better treat the symptoms of the disease.

History

To illustrate the marked change in the tempo of research that has occurred in PD we need only look at the chronology of the various markers of our understanding of the disease.

In 1817 James Parkinson published the manuscript that first clearly described the disorder. His monograph, parenthetically, noted the limitation of clinical observations and stressed that pathologic confirmation of his observations was necessary. Yet it took another hundred years for the neuropathology to be characterized, with the reports of Tretiakoff describing the loss of pigmented neurons in the pars compacta of the substantia nigra² and of Lewy describing the presence of round eosinophilic bodies both in and outside neurons in the same region.³ The implications of these neuropathological changes were debated over the next several decades and it was not until the mid-1950s that the importance of the nigral degeneration was universally accepted.⁴ The controversy centered on whether changes in the striatum (putamen and caudate nucleus) accounted for the signs of parkinsonism and thus represented the most important locus of de-

generation. This is interesting because current dogma holds that the striatum is completely spared in PD. Only in the last decade has the Lewy body been made a neuropathological requirement for the diagnosis of PD.

The great epidemic of lethargic encephalitis (von Economo), which peaked between 1917 and 1923, continued producing cases through the 1930s.⁵ It helped clarify the neuropathology of PD⁴ and simultaneously spurred interest in developing a theory of PD etiology. It is easy to understand that one form of parkinsonism, namely post-encephalitic (PEP), clearly caused by an infectious illness, looked so much like another form, idiopathic PD, which had a viral-like inclusion body in its histopathology that theories of a viral causation would spring to mind. It is as unclear now as it was to researchers at the time why anyone would link PD and PEP since the pathologic changes were so different.⁶ Yet, in 1961, Schwab and Poskanzer published their paper predicting the end of PD by 1980.⁷ It was a milestone in formulating, perhaps for the first time, a cogent theory of PD etiology. As incorrect as it was, it still provides a model for the bold assertion of a testable hypotheses of disease causation.

... a breakdown product of MPTP causes mitochondrial dysfunction in the neurons that secrete dopamine.

In 1960 the marked deficiency of dopamine was recognized⁸ and in 1965 the first beneficial levodopa trials were reported.⁹ By the 1970s amantadine was found to be helpful,¹⁰ and dopamine agonists were being developed (anticholinergics had been recognized as beneficial from the turn of the century or before).

Over the last 10 years our approach to understanding and treating the disease has been changed by the discovery of 1-methyl-4-phenyl-L, 2, 5, 6-tetrahydropyridine (MPTP),¹¹ the narcotic "designer drug" that kills pars compacta nigral neurons. This discovery led to the development of the first good primate animal model of PD. Infusions of MPTP into

primates cause similar lesions and clinical signs as they do in humans.¹² Infusions into one carotid artery even produces unilateral parkinsonism. Intense research into the mechanism of action of MPTP led to the discovery that a breakdown product of MPTP causes mitochondrial dysfunction in the neurons which secrete dopamine.¹³ This furthered the hypothesis, discussed below, that oxidative phosphorylation defects lead to PD and that PD may be an example of an environmental toxin-causing disease in a predisposed person.¹⁴

Current Treatment

While the treatment of PD is clearly better now than it has ever been, it is still far from satisfactory. The backbone of therapy remains levodopa, the efficacy of which requires its conversion to dopamine, which can only occur within the remaining nigral neurons. Thus, as the disease progresses and more neurons die, fewer remain to convert the levodopa to dopamine, leading to a decline in drug response. Although the dopamine agonists bromocriptine and pergolide act directly on the dopamine receptors, bypassing the dead and dying neurons, these drugs appear to have an efficacy directly related to the amount of dopamine available. When the disease is advanced and little dopamine is available, despite the addition of levodopa, the dopamine agonists don't work either.

The majority of PD patients treated with levodopa develop dyskinesias, clinical fluctuations, or other problems within 5 years. An important question, debated for 2 decades and still not answered, is what role levodopa plays in the generation of these drug side effects? Is the appearance of dyskinesia, dystonia, wear-

ABBREVIATIONS USED

ALS: Amyotrophic lateral sclerosis

CAT: Computed axial tomography

MAO: Monamine oxidase (inhibitor)

MPTP: 1-methyl-4-phenyl-L,2,5,6-tetrahydropyridine

NMDA: N-methyl-D-aspartate

PD: Parkinson's disease

PET: Positron emission tomography

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ing off or on-off due to advanced disease or to levodopa exposure? If one believes that duration and dose of levodopa contribute to the long-term problems in management then levodopa is withheld until the patient "needs it." On the other hand, if levodopa is thought to cause its problems only when the disease has advanced to a certain degree then obviously the drug should be introduced early and used maximally until the side effects appear. Adding fuel to the debate is the free radical hypothesis of disease etiology that proposes that a deficiency in the neuron's ability to clear free radicals leads to lipid peroxidation and cell breakdown. Since the metabolism of dopamine produces free radicals, the use of levodopa stimulates this process, implying the possibility that levodopa actually hastens disease progression even as it improves symptoms.

Clozapine lacks extrapyramidal side effects and thus is the only antipsychotic that can be used to treat psychosis in PD patients without worsening the parkinsonism.

The Parkinson Study Group has used the free radical theory as a clinically testable hypothesis by testing two drugs that reduce free radical production in PD in a large group of mild, untreated PD patients to see which, if any, group progressed more slowly. The drugs, deprenyl (selegiline), which slows the degradation of dopamine by blocking monoamine oxidase b, and vitamin E (tocopherol), which is a "free radical scavenger," were used alone and in combination and were compared to placebo. Progression was measured as the time taken, from entry into the study, until levodopa was required for symptomatic relief. The initial results¹⁵ clearly favored deprenyl and suggested the possibility that deprenyl, although providing a small symptomatic benefit, slowed disease progression. This interpretation was challenged¹⁶ and more recent results, of a longer observation period¹⁷ shows a parallel decline in the treated versus untreated groups, suggesting a symptomatic rather than a "protective" benefit. A pathological study¹⁸ demonstrated that fewer neurons had degenerated in deprenyl treated patients as compared to untreated PD patients, implying a true protective effect, however.

Whether deprenyl retards disease pro-

gression or not, it unequivocally delays the time until levodopa is required.^{15,17} For physicians who believe that delaying levodopa is a good thing, it therefore makes sense to initiate deprenyl at the time of diagnosis in young patients whose symptoms are mild enough to not require levodopa. There are no data to guide a decision about the joint use of levodopa and deprenyl in slowing disease or disability progression.

Another new drug found to be helpful but not developed or approved specifically for use in PD is the atypical antipsychotic clozapine. This drug lacks extrapyramidal side effects and thus is the only antipsychotic that can be used to treat psychosis in PD patients without worsening the parkinsonism.¹⁹ Since psychosis occurs as a dose-limiting side effect of PD medications in up to 20% of patients followed long-term, this drug has an important place in treatment since alternative approaches to management of psychosis require a reduction in drug or use of a neuroleptic, both of which cause worsened parkinsonism. Interestingly, clozapine not only is well tolerated, without worsening parkinsonism, but has been reported to improve both PD tremors²⁰ and levodopa-induced dyskinesias.²¹

Current Research

Etiology

Identifying the cause of PD is the most important single goal of current research since this should lead to prevention and arrest of disease progression. There is data to suggest an abnormality of oxidative-phosphorylation in neuronal mitochondria of PD patients.^{13,14,22} This finding fits with the free radical theory of PD etiology but more work needs to be done to confirm that this is a reliable finding that is relevant to the disease and not simply an epiphenomenon.

Studies looking for a genetic component in PD are also underway. Although old reports showing no increase in concordance of PD in identical twins are often cited as evidence against a genetic theory of PD etiology,²³ a recent follow up²⁴ found that unaffected monozygotic twins had evidence of subclinical dopamine deficiency, as measured by PET scan in 45% (4 of 9) of cases while the number was 29% in dizygotic twins. Yet only one monozygotic pair was concordant for clinical PD. Thus, one twin study suggests a possible genetic predisposition

for this disease. Further twin studies are in progress now.²⁵ Other research looking for a genetic cause involves studies of patients with familial PD.

Treatment

Although adrenal implants have been shown to be not helpful,²⁶ fetal implants look somewhat more promising.^{27,29} Results, however, are by no means convincing.³⁰ This work has proceeded slowly because of fiscal and other constraints. At this point it is unclear what type of PD patient will benefit, how much fetal tissue needs to be implanted, whether the fetal tissue should be inserted in small blocks or as a suspension, where the tissue should be inserted, whether immunosuppression is required or even whether the improvement is due to the implant rather than the trauma of the procedure.³⁰ Furthermore the disease process itself is active and its effect on the fetal tissue remains to be seen. So far only one fetal implant patient has come to autopsy, and although living implant tissue was found, no dopamine secreting cells were alive.³¹

Another promising implant approach uses an encapsulation technique in which the desired cells are encased in a semipermeable membrane that allows neurotransmitters and other chemicals to diffuse out but inhibits any immune response.³²

This approach appears to allow cells from unrelated species to be implanted and to function as chemical factories in the host without rejection despite the lack of immunosuppressive therapy. Using genetically engineered pheochromocytoma line cells, one can choose how many cells to encapsulate in order to provide the desired amount of dopamine to the target area. The cells are encapsulated in spaghetti-like filaments and are placed via stereotactic surgery. They work well in primates but have yet to be tested in humans.

. . . as the disease progresses and more neurons die, fewer remain to convert the levodopa to dopamine, leading to a decline in drug response.

An old surgical technique for the treatment of PD symptoms has recently been resurrected and early results appear promising.^{33,34} Pallidotomy, a technique in which a small hole is placed in the internal segment of the globus pallidum, reportedly improves bradykinesia, rigidi-

ty, and tremor while simultaneously reducing levodopa-induced dyskinesias. This procedure had been abandoned in the pre-CAT scan era because of two factors: 1) Stereotaxis was not accurate so that the risk of morbidity was high; and 2) the surgical results from the pre-levodopa era looked mainly at tremor as the response variable.

Since thalamotomy is easier and safer than pallidotomy and works better at controlling tremor, pallidotomy was supplanted by thalamotomy, which remains the most effective treatment for tremor when drugs fail. Recent animal experiments buttress support for pallidotomy, which reduces slowness and rigidity in primate models of PD.^{35,36} Since surgery has a small but clear morbidity attached to it and precludes a double blind controlled trial it is difficult to evaluate. An open trial, using the gamma knife to create the pallidal lesion, in preparation for a definitive double blind placebo controlled trial, is currently underway in the Brown University Department of Clinical Neurosciences.

Active areas of research involve a large number of dopamine agonist trials sponsored by various pharmaceutical concerns. A new mono-amine oxidase b inhibitor is under evaluation.³⁷ Blockers of the enzyme, catechol-o-methyl transferase, that metabolizes dopamine, are being tested as well.

Novel approaches either being tested or considered include GM1 ganglioside,⁵⁸ glutamate antagonists,³⁹ neural growth factors,⁴⁰ dopamine transporter blockers,⁴¹ and inhibitors of the "a" form of mono-amine oxidase. In a report that garnered a large amount of media attention,³⁸ GM1 ganglioside, a normal constituent of brain was given on a chronic basis to monkeys rendered parkinsonian by MPTP. It was intended to "stabilize injured or dying nigral dopamine neurons and perhaps stimulate sprouting of new dopaminergic fibers." The benefit

of the GM1 ganglioside is relatively non-specific and has been used in other neurologic disorders affecting both the central and peripheral nervous systems. The benefit in MPTP monkeys was impressive clinically but not chemically or pathologically. Human trials are expected to be underway shortly.

The rationale for blocking glutamate receptors³⁹ rests on both the observation that blockade of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor prevents the toxic affects of MPTP in animals and the hypothesis that excitatory amino acid neurotransmitters, such as glutamate, may be overly active in PD, causing the death of neurons by overstimulation. In fact, NMDA blockers, such as amantadine, and possibly dextromethorphan, ameliorate symptoms of PD aside from the theoretical possibility of slowing disease progression.

Pallidotomy, a technique in which a small hole is placed in the internal segment of the globus pallidus, reportedly improves bradykinesia, rigidity, and tremor while simultaneously reducing levodopa-induced dyskinesias.

The dopamine transporter is a protein specific to dopamine secreting cells that transports dopamine across the neuronal membrane from the outside. It is also responsible for transporting the neurotoxins MPTP and 6-hydroxydopamine, which specifically poison dopaminergic cells. If naturally occurring toxins cause PD, then blocking the transporter might retard disease progression.⁴¹ This also could improve PD symptoms by increasing the amount of dopamine in the synaptic cleft. One drug that blocks the dopamine transporter was reported to improve parkinsonism in a short study.⁴²

Neurotrophic factors have been found which decrease superoxide radicals and increase dopaminergic neuronal projections in cell cultures.⁴¹ These factors have been hypothesized as explaining the improvement that did occur in the adrenal-implanted PD patients. Neurotrophic factors are used in ALS clinical experimental trials, but not yet in PD.

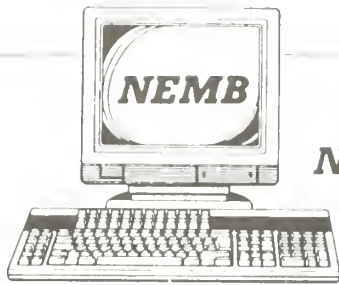
Since MAO-a is the predominant MAO enzyme in the dopamine neuron, trials of selective MAO-a inhibitors may work better than selegiline in reducing free radical production. Unlike the MAO-b inhibitor, however, these drugs may be difficult to use because of the possibility of inducing hypertensive crises, especially in patients taking levodopa.

A novel approach to treating symptoms is the use of an electrical stimulator. An electrode placed in the thalamus has been reported to arrest tremor contralaterally when attached to a stimulator, thus "overdriving" the thalamus without an ablative lesion.⁴³ A similar technique evidently ameliorates bradykinesia when the stimulating electrode is placed in the subthalamic nucleus.⁴⁴

This brief review provides a snapshot of where we stand now. The number of approaches seems to expand exponentially year by year providing us with more opportunities but undoubtedly with more false leads. Choosing which paths to pursue first will be difficult until one or more causes for PD are clearly identified.

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Huntington's Disease: New Insights into a Hereditary Disorder

Brian R. Ott, MD

Huntington's disease (HD) is an autosomal dominant hereditary neurologic disorder characterized by progressive chorea, behavioral disturbance, and dementia. Among dementing illnesses, HD accounts for 2% to 3% of cases in series of patients evaluated at dementia units. Using published prevalence rates, an estimated 40-70 persons are afflicted with the disease in Rhode Island at any one time. Males and females are equally affected.¹

Hereditary chorea was reported as early as 1860, but it was not until the landmark description of a cohort of families in East Hampton, Long Island by George Huntington in 1872² that the disease received widespread recognition. Ancestors of Huntington's original patients were traced to immigrants from England who landed in the Atlantic colonies in 1649. Other cases in South Africa, Venezuela, and Tasmania have also been traced to ancestors from Europe. Spontaneous mutations outside of this common source are felt to be rare or nonexistent.

The past 10 years have seen significant breakthroughs in our understanding of the pathogenesis and genetics of this incurable and fatal disease.

Clinical Manifestations

The most common presenting feature is personality change. Patients may manifest apathy, loss of personal hygiene, impaired judgment, and inappropriate or antisocial behavior. Psychiatric disturbances are common. Half of patients may have evidence of depression; suicide accounts for about 7% of deaths. Another quarter of patients have evidence of psychosis marked by delusions and hallucinations.¹

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Although usually occurring shortly after the onset of movement disorder, the dementia syndrome of HD may precede chorea by several years. Early cognitive impairments include word-finding difficulty as well as recent and remote amnesia. Fluent aphasia, agnosia, and apraxia, typical of Alzheimer's disease, are usually absent. As the disease progresses, frontal lobe deficits become prominent including impaired judgment, concentration, planning, and sequencing abilities. The early manifestations of chorea appear as facial grimaces and brief involuntary, non-purposeful and non-repetitive finger movements, which may resemble tics but are slower. The choreic movements may be suppressed momentarily, and they subside in sleep. Dysarthric speech is common. As the disease progresses the movements become more pronounced and affect the entire body

... an estimated 40 to 70 persons are afflicted with the disease in Rhode Island at any one time.

including the trunk. The gait is characterized by writhing and lurching movements. Involuntary movements become slower and blend together in an athetotic appearance. Dystonic postures occur. Dysphagia is common, and may lead to frequent aspirations. Terminally, the patient is rigid and mute.

In a patient with the typical clinical features of personality disorder, dementia, and chorea as well as a positive family history, the diagnosis of HD is not difficult. Occasionally, however, patients are encountered who have chorea but lack a family history for the disease. In addition to HD there are more than 150 neurologic disorders in which chorea is a feature.³ The more common disorders are listed in Table 1.

Age at Onset

The average age of onset is 35 to 45 years with a range of 10 to 70 years; the

In the absence of effective treatment, the ethics of diagnosing the disease in asymptomatic persons has been questioned.

average course is 10 to 15 years from onset of symptoms to death, usually as the result of secondary illness such as pneumonia. There is variance in disease expression according to the age of onset. Among the 3% to 10% of cases with onset prior to age 20, ie, juvenile form, rigidity, parkinsonian type tremor, and dystonia are more often seen than chorea, and seizures occur in about half of cases. Cerebellar signs may also be seen. Those with early onset appear to have a more rapidly progressive course. For reasons that are not understood, inheritance in early cases is usually through the father. Late onset cases beginning after the fifth decade follow a more prolonged course, and the severity of dementia is less. Late onset cases are more often inherited from the mother.

Pathology and Neurochemistry

Gross changes of the brain include atrophy of the frontal and parietal lobes, thalamus, caudate nucleus, globus pallidus, and putamen. Gliosis is usually seen in the caudate and putamen (the striatum), where microscopically, neuronal loss is most severe involving loss of small and medium-sized neurons that are important for inhibition of movement. Neuronal loss in cerebral cortex and thalamus probably contribute to dementia, although there is some controversy about the extent of involvement of these structures in HD.

CT and MRI scans reveal atrophy of the caudate nuclei, but are usually normal in early and presymptomatic individuals. The lateral walls of the anterior horns of the lateral ventricles show a flat or convex appearance. Abnormalities in caudate nucleus metabolism and blood flow can be seen at an earlier symptomatic stage as well as in some presymp-

ABBREVIATIONS USED:

CT: Computerized tomography
DNA: Deoxyribose nucleic acid
GABA: Gamma amino butyric acid
HD: Huntington's disease
MRI: Magnetic resonance imaging
PET: Positron emission tomography

tomatic individuals by the use of positron emission tomography (PET) scans of the brain.⁴ The primary neurotransmitter for the striatal cells is GABA, which acts to counterbalance the stimulating effect on movement by dopaminergic neurons. The nigrostriatal dopaminergic pathway, which is lost in Parkinson's disease, is preserved in HD.

Other neurotransmitters are deficient in the HD brain, including acetylcholine, enkephalin, and substance P. Like the dopamine pathways, neuronal circuits using the peptide neurotransmitter somatostatin are preserved, and somatostatin levels are elevated.^{5,6} The clinical utility of this observation is an area of active investigation.

Genetic Issues

Huntington's disease is inherited in an autosomal dominant fashion with complete penetrance. Consequently all persons with the gene and half of their offspring can be expected to develop the disease. The genetic impact of the disease on families has led to a thrust in research to develop a diagnostic test for presymptomatic individuals. Because family development usually precedes symptom onset, and because of the difficulties encountered in managing the personality disorder of HD patients, genetic counseling has been problematic.

In the mid 1980s recombinant DNA technology led to the discovery of a DNA marker linked to the gene for HD.⁷ The gene for HD appeared to be located on the short arm of chromosome 4. Further development of this technology^{8,9} has enabled research centers such as Massachusetts General Hospital to offer predictive testing for HD during the past several years.¹⁰ The accuracy of positive and negative tests is as high as 95%; however, in about 5% to 10% of cases the test is non-diagnostic.

In a patient with the typical clinical features of personality disorder, dementia, and chorea as well as a positive family history, the diagnosis of HD is not difficult.

In the absence of effective treatment, the ethics of diagnosing the disease in asymptomatic persons has been questioned. Fears have been raised that conveying such information to individuals who are at risk for major depression may in itself lead to depression or even sui-

Table 1.—Common Causes of Chorea

Hereditary

Huntington's disease
Wilson's disease
Benign familial chorea
Choreoacanthocytosis

Developmental and age related

Cerebral palsy
Kernicterus
Senile chorea

Metabolic and endocrine

Chorea gravidarum
Hyperthyroidism
Hypoparathyroidism

Drug induced and toxic

Anti-parkinson drugs, eg
levodopa
Anticonvulsants, eg phenytoin
Antipsychotics, eg haloperidol
Steroids, eg oral contraceptives

Infectious and immunological

Sydenham's chorea (post-streptococcal)
Viral encephalitis
Systemic lupus erythematosus

Cerebrovascular

Basal ganglia stroke
Subthalamic nucleus stroke

cide. Other issues that must be dealt with by the person who is told of a positive result include potential job and insurance discrimination, anxiety over future planning, and guilt feelings over transmission to offspring already born.

To address these concerns, a study was recently published in which 135 subjects, including 112 who received genetic testing for HD, were assessed for depression.¹¹ Not surprisingly, those who were told that they had a low risk of disease showed a lowered degree of psychological distress and depression 6 and 12 months after baseline measurements were obtained. Those for whom there was no change in their risk showed no change in the psychological measures. Most importantly, among those who were told that they were at increased risk for disease, there was an actual decline in stress and depression. There were no suicides and no psychiatric hospitalizations.

These results suggest that for some people at risk for HD, getting an answer, be it good or bad, conveys psychological benefit. For those with knowledge of a high risk for disease, planning for the future may be seen as the alternative to worrying about the uncertainty of the future.¹²

Administration of the present form of genetic linkage testing is complex and

requires participation of many affected and unaffected family members. Preferably both parents and another affected family member are included in the genetic test. This degree of cooperation may be difficult, particularly for families who have kept the disease a "secret" in past generations. Such testing is not possible for individuals without known affected family members.

In March 1993, the Huntington's Disease Collaborative Research Group announced the identification of the HD gene.¹³ This discovery should lead to a simpler blood test of the at-risk individual as well as greater accuracy in predicting risk of disease. The next step in this area of research is to define the function of the protein that is expressed by the gene mutation. An understanding of how this protein produces the specific disease manifestations may then lead to an avenue of treatment.

Treatment

It is also hoped that treatment effective in slowing or halting the pathologic process of HD will result from research into the mechanisms of neurodegeneration. Clinical trials may be developed some day using drugs that influence nerve growth factors in the brain or the damaging effects of certain amino acids.

Abnormalities in caudate nucleus metabolism and blood flow can be seen at an earlier symptomatic stage as well as in some presymptomatic individuals by the use of positron emission tomography scans of the brain.

For example, glutamate has been shown *in vivo* to be capable of causing neuronal death, and some researchers believe that it may be an important proximate mediator of cell death in HD.¹⁴ Although there is no exact animal model for HD itself, injections of a neurotoxic substance called kainic acid into the striatum of rats produces abnormalities of movement and learning that parallel the symptoms of HD. Decortication of rats before such injections causes degeneration of striatal afferents containing excitatory transmitters such as glutamate, and protection against the toxic effect of kainic acid.¹⁵ If this mechanism of excitotoxicity is important in HD, then treatment aimed at interfering with the cellu-

lar receptors for glutamine may retard disease progression or prevent its development in patients identified to be at risk by genetic testing.

Currently, the treatment of HD is symptomatic. Haloperidol and phenothiazine drugs are often used to control chorea as well as irritable or psychotic behavior; however, the development of tardive dyskinesia, dystonia, and rigidity often limits the usefulness of this type of intervention. The mode of action of such agents is via blockade of the dopamine receptors that promote choreiform movement. Treatment with GABA-ergic and cholinergic drugs has been disappointing so far.

Efforts have recently begun to form a Rhode Island regional support group for HD. Interested persons should contact Thomas Vescera, 31 Oneida Street, Pawtucket, RI. Telephone (401)724-9622.

The cognitive impairments of the disease are not helped, and may even be worsened, by neuroleptic drugs. Depression responds to fluoxetine, tricyclic agents, lithium, and electroconvulsive therapy. Anxiety may be treated with benzodiazepines.

Psychological and social support systems are necessary for the comprehensive management of the patient with HD. Efforts have recently begun to form a Rhode Island regional support group for HD. Interested persons should contact Thomas Vescera, 31 Oneida Street, Pawtucket, RI, phone 724-9622.

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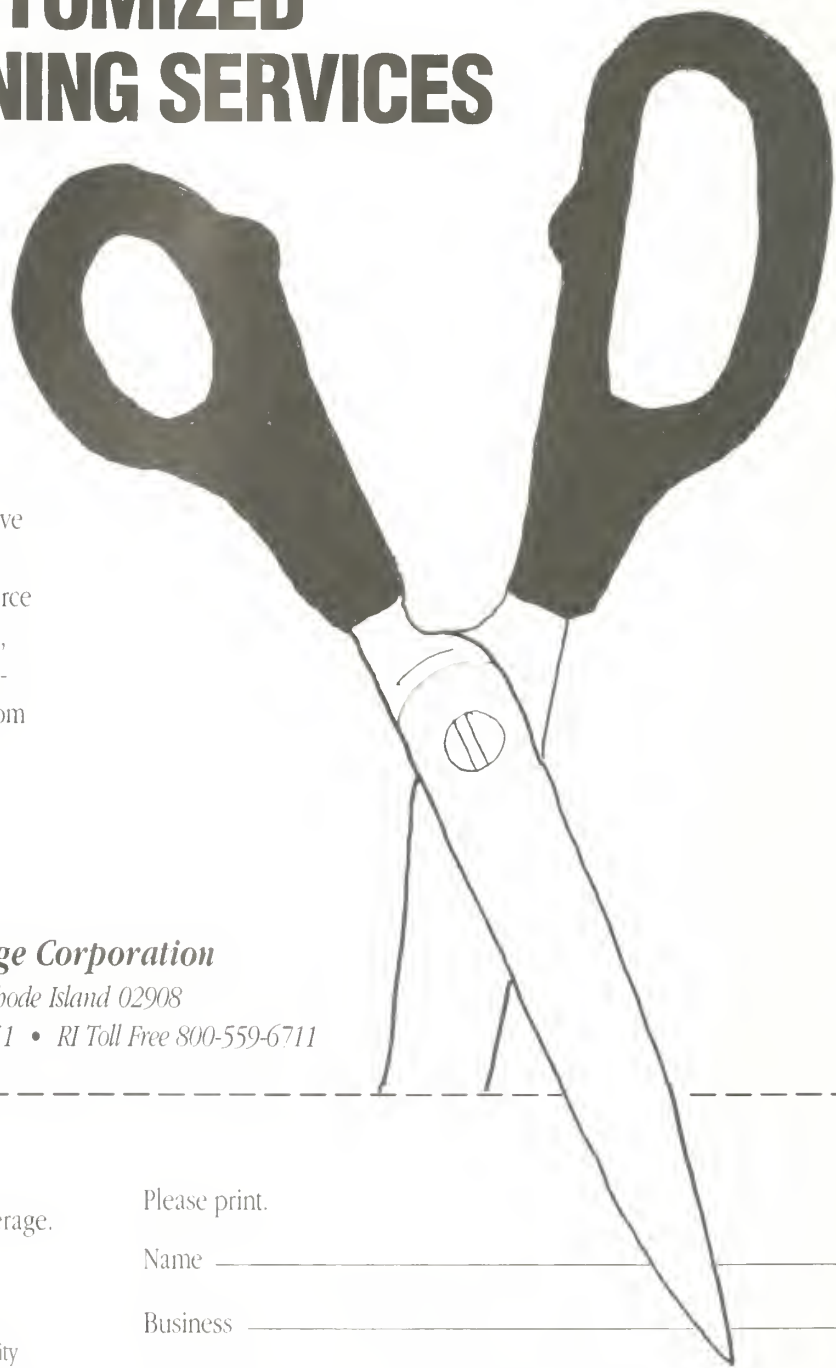
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Neuropsychiatric Aspects of Movement Disorders

Stephen Salloway, MD, MS

Neuropsychiatry involves assessing and managing psychiatric problems that develop in patients with known or suspected neurological illness. Studying the behavioral disorders seen in patients with brain disease has provided important clues for understanding the neurological basis of idiopathic psychiatric illnesses such as depression, schizophrenia and obsessive compulsive disorder (OCD). Early workers in neuropsychiatry were trained in psychiatry, neurology, and neuropathology. Landmark discoveries were made in the late 19th century by Alzheimer, Wernicke, Charcot and others who mapped out important language areas in studying aphasia, described the behavioral manifestations of neurosyphilis and identified the degenerative and vascular dementias. Neuropsychiatry fell into disfavor when psychoanalysis shifted the focus of psychiatry from neuropathology to the study of the role that psychological factors play in causing mental illness.

Movement Disorders and Neuropsychiatric Illness

Advances in structural and functional brain imaging and molecular neurochemistry during the past decade has reinvigorated neuropsychiatry. Despite our improved technological tools, significant challenges remain for clinical researchers trying to draw valid conclusions about the pathogenesis of behavioral abnormalities seen in neurological patients.

For example, how do we determine if the depression seen in Parkinson's disease (PD) is caused by the loss of neurons critical for the maintenance of normal mood or by the patients' reaction to living with a chronic debilitating illness?

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Most studies have shown that depression is more common in PD than in age-matched controls and in patients with other chronic illnesses who have a similar level of disability.¹ However, at least one study found no difference in the severity of depression between patients with PD and rheumatoid arthritis.² The motor deficits in PD are caused by the loss of dopaminergic neurons. Does the loss of dopamine also cause the mood and cognitive changes that are common features of the illness or is some other neuropathological process involved?

The answers are not simple because psychiatric symptoms in neurological patients are usually related to multiple factors. Careful research design, appropriate animal models and standardized measurement techniques with relevant control groups are essential for obtaining meaningful answers to these complicated questions.

This paper will discuss the neuropsychiatric aspects of three common movement disorders: Parkinson's disease, Huntington's disease and Tourette's syndrome and briefly review the area of psychogenic movement disorders. Parkinson's disease, Huntington's disease and Tourette's syndrome were chosen because they demonstrate how closely psychiatry and neurology are related. While each of these syndromes is known for its characteristic movement abnormalities, the incidence of comorbid psychiatric symptoms is high. The psychiatric symptoms may precede the abnormal movements and may become the most disabling feature of the illness. It is important for physicians to be aware of the psychiatric aspects of the movement disorders in order to provide effective treatment and informed guidance for family members.

The subcortex, basal ganglia and upper brainstem contain vital structures for the regulation of mood, cognition and movement. The extrapyramidal motor system and key behavioral circuits follow closely related parallel pathways as

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they course from the midbrain and relay in the striatum and thalamus en route to their separate effector sites in the frontal lobe (Figure 1). The principal neurotransmitter appears to be the same for both systems at each level. Movement disorders provide a model for studying the organization of the basal ganglia and for probing the relationship between behavior and motor systems in these important frontal-subcortical circuits.

Parkinson's Disease

The main psychiatric complications in Parkinson's disease are depression, anxiety, dementia, psychosis, confusion, and subtle neuropsychological deficits. About 40% of parkinsonian patients develop depression.³ About half of these have a major depressive disorder and the other half have symptoms of chronic low-grade depression or dysthymia. (Dysthymia is less severe in intensity than major depression and is present for at least 2 years without prolonged remission.) The masked facies of PD causes the appearance of a constricted affect that can make patients appear depressed, when they are not. Dopamine deficiency can also cause apathy and psychomotor retardation mimicking depression,^{4,5} and it is important to ask patients directly about their mood.

The neurochemistry and neuroanatomy of depression in PD has been an active area of research. Mayberg et al have shown a decrease in metabolism in the inferior frontal lobe in PD patients with depression.⁶ Dopamine depletion is

ABBREVIATIONS USED

ECT: Electroconvulsive therapy

HD: Huntington's disease

5-HIAA: 5-Hydroxyindole acetic acid

OCD: Obsessive compulsive disorder

PD: Parkinson's disease

PET: Positron emission tomography

TS: Tourette's syndrome

the neurochemical hallmark of PD, but the monoaminergic transmitters norepinephrine and serotonin, as well as other neurotransmitters, are also decreased to some extent in PD. Some patients report an increased sense of well-being on levodopa, but levodopa alone does not appear to be an effective antidepressant. Mayeux et al and others have demonstrated that PD patients with major depression have lower levels of the serotonin metabolite 5-HIAA in their spinal fluid than dysthymic and non-depressed PD patients, suggesting a serotonergic deficit in major depression in PD.³ McCance et al induced a transient depressive reaction by depleting the serotonin precursor tryptophan in a patient with PD and depression. The depression was quickly reversed by restoring tryptophan to the diet,⁷ supporting the hypothesis that serotonin deficiency is important in PD depression.

Anxiety also may be a common problem in PD.⁸⁻¹⁰ Hilde Bruch, a noted psychiatrist with PD, eloquently described the personality change she experienced when she developed PD.¹¹ She stated that she had always been a calm person, but that as the PD progressed, she noticed that she began to shake whenever there was the least bit of uncertainty and that she often became annoyed or anxious over minor matters. Some patients go on to develop panic attacks late in life. Autopsies conducted on a small group of PD patients with and without panic disorder

... how do we determine if the depression seen in Parkinson's disease is caused by the loss of neurons critical for the maintenance of normal mood or by the patient's reaction to living with a chronic debilitating illness?

der found an association between panic anxiety and prominent loss of noradrenergic neurons from the locus ceruleus in the pons (Schiffer and Folstein, personal communication).

Depression in PD can be a major cause of distress and disability and should be treated. Only a few placebo-controlled trials have been carried out for the treatment of depression in PD, and no data exists concerning the relative efficacy of different antidepressants. Clinicians should consider the side effect profile in

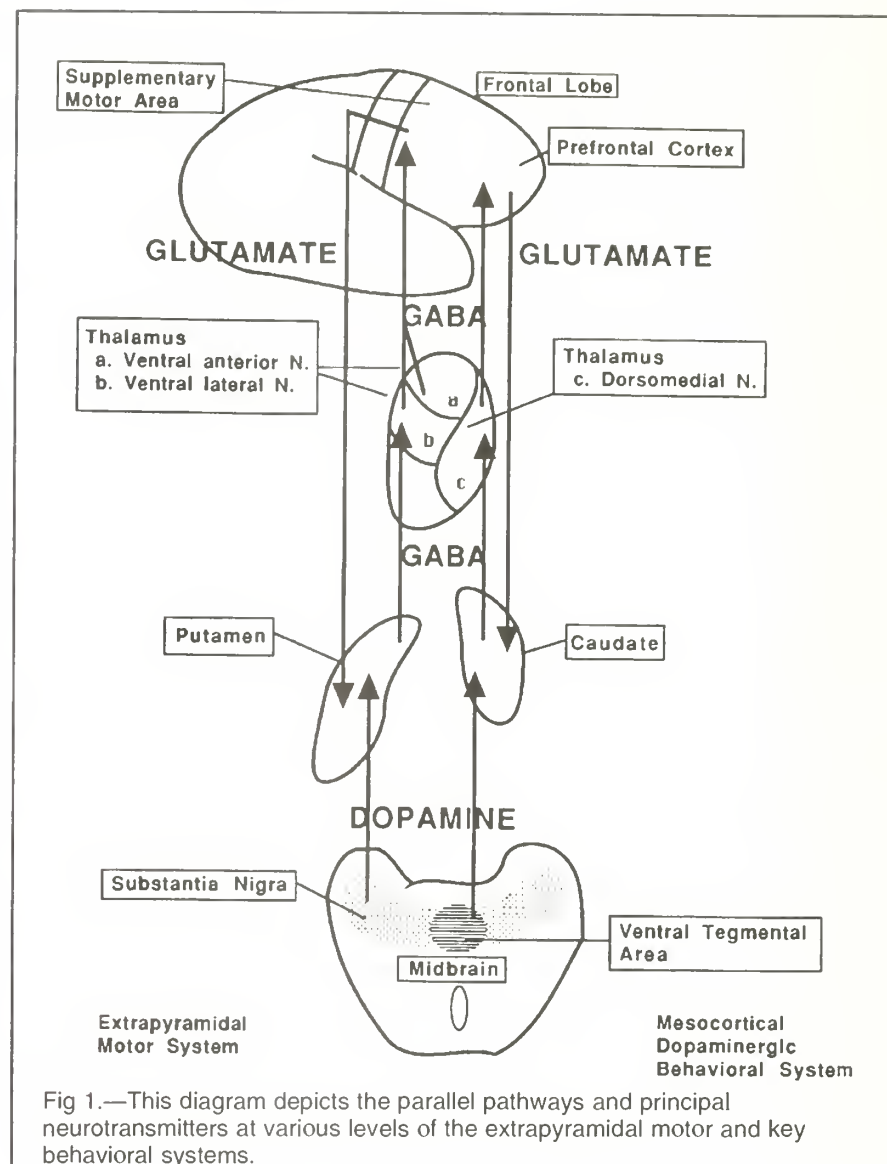


Fig 1.—This diagram depicts the parallel pathways and principal neurotransmitters at various levels of the extrapyramidal motor and key behavioral systems.

choosing an antidepressant. PD patients are sensitive to the side effects of antidepressants and may respond to lower doses. Some patients obtain mild motor improvement from the anti-cholinergic effects of the tricyclic antidepressants. The newer antidepressants that block serotonin reuptake can cause dyskinesia, induce akathisia and can exacerbate anxiety. ECT may help relieve depression and transiently improve motor symptoms but PD patients are at greater risk for developing post-ECT delirium.

Cognitive Impairment in Parkinson's Disease

About 20% of PD patients develop Alzheimer's type dementia.¹² Plaques and tangles are abundant in the brain, and there is a marked dropout of cholinergic

neurons from the Nucleus Basalis of Meynert. A large proportion of PD patients without dementia will have more subtle neuropsychological deficits.¹³ Loss of dopamine probably plays a role in the development of the psychomotor retardation commonly seen in PD. Trevor Robbins (personal communication) has found that mental speed slows down in PD patients off levodopa replacement and increases once the levodopa has been reinstated. Patients with PD have trouble changing cognitive set and tend to perseverate on cognitive tasks that require mental flexibility. Other cognitive problems in PD are difficulty with time sequencing and a decrease in visuospatial ability. Trouble with sequencing may make it difficult for patients to comply with their complicated medication regimen.

Confusional states or psychosis occur at some point in 33% of patients with PD. Problems with confusion and psychosis in PD are usually a side effect of dopamine replacement and concomitant treatment with anticholinergic agents. Two types of mental state change have been described.¹⁴ In one type, the sensorium is clear, but visual and rarely auditory hallucinations occur and paranoia is common. The second type is more characteristic of delirium with disorientation, confusion, and disinhibited behavior. The dose of the dopamine replacement and augmentation therapy should be decreased and use of other drugs that can cause psychosis or delirium should be reevaluated. Some patients can not tolerate a decrease in their dopamine therapy. Treatment with antipsychotics, such as haloperidol, may worsen motor performance. Clozapine, a novel antipsychotic agent, may be effective in low doses and does not cause parkinsonism.

Neuropsychiatric Problems in Huntington's Disease

Huntington's disease (HD) is characterized by the triad of chorea, dementia, and behavior change. (See preceding article in this issue.) Depression occurs in 44%, intermittent explosive disorder in 35%, alcoholism in 15% and mania in 10%.¹⁵ Schizophreniform psychosis and obsessive-compulsive disorder are less common. Suicide attempts and depression often precede the chorea and the diagnosis of HD implying that depression is often an intrinsic feature of the disease rather than simply a reaction to a fatal degenerative illness. The first cell

Suicide attempts and depression often precede the chorea and the diagnosis of HD, implying that depression is often an intrinsic feature of the disease rather than simply a reaction to a fatal degenerative illness.

loss in HD is seen in the medial caudate, which may correlate with the early appearance of depression. The medial caudate is richly connected to the frontal lobe and the amygdala. Mayberg et al have shown that HD patients with de-

pression have decreased metabolism in the inferior frontal lobe on PET scanning.¹⁶ These findings support the growing body of evidence showing that depression and mania may follow strokes in the caudate.

The dementia of HD is often referred to as a subcortical dementia.¹⁷ Mental functions thought to reside primarily in the cortex such as aphasia, agnosia, and apraxia are usually absent early in the illness. Patients characteristically develop slowness of thought, a decreased ability to abstract and concentrate, difficulty carrying out a sequential task, motor impersistence and impaired memory that improves with cueing.^{16,18} They may be easily overwhelmed and confused, and they may have labile emotions that alternate between apathy and irritability and euphoria.

Cognitive impairment may also be due to loss of neurons in the caudate nucleus causing disruption of frontal lobe-subcortical connections. Sorting out the cause of the dementia can be difficult. Generalized atrophy can occur in the cerebral cortex and focal cell loss from specific layers of the dorsolateral prefrontal cortex may be seen as the disease progresses.¹⁹ The cognitive decline could therefore be caused by a combination of cortical and caudate degeneration.

The dopamine antagonists like haloperidol can help treat psychosis and suppress the chorea. They may worsen cognitive slowing and cause unacceptable stiffness. Depression should be treated with antidepressant medication. At times, ECT is necessary. Lithium may be indicated for manic episodes, watching for side effects. Impulsive and aggressive behavior can be difficult to control. Neuroleptics, benzodiazepines, carbamazepine, sodium valproate and buspirone can be tried.

Tourette's Syndrome

Tourette's syndrome (TS) is a childhood onset movement disorder characterized by vocal and motor tics. (See article in this issue.) The comorbid incidence of psychiatric and behavioral disturbance in TS has been widely debated. About 20% of patients with TS also meet strict diagnostic criteria for obsessive-compulsive disorder (OCD) and a total of 30% to 50% has prominent symptoms of OCD. First-degree relatives of TS patients have a 13% incidence of OCD

compared to 1% to 2% in the general population. Pauls and Leckman²⁰ provided preliminary evidence that TS and OCD share a similar genetic locus. Attention deficit hyperactivity disorder is another common problem in individuals with TS. There is a disagreement about the incidence of other behavioral disorders such as conduct disorder, affective disorder and anxiety syndromes in TS. Intelligence appears to be normal but may be limited by attentional problems.

Autopsies conducted on a small group of PD patients with and without panic disorder found an association between panic anxiety and prominent loss of noradrenergic neurons from the locus ceruleus in the pons.

The tics can be suppressed by high potency dopamine-blocking drugs such as haloperidol, though this may lead to unacceptable side effects such as stiffness, mental dullness, anergia, depression and tardive dyskinesia. Psychostimulants may help improve attention but can exacerbate the tics. OCD and depression can be treated with serotonin-reuptake blocking drugs such as clomipramine, fluoxetine, and sertraline. Lithium or carbamazepine may help with mood lability. Behavior therapy and a carefully structured educational program are often essential adjunctive measures.

Conceptualizing the tics as compulsory motor acts may provide a framework for linking tics and OCD. The neuroanatomical basis of TS and OCD have not been clearly elucidated, though there are some clues. The anterior cingulate gyrus and the head of the caudate nucleus show evidence of hypermetabolism on PET in untreated OCD,²¹ and there may be subtle structural abnormalities in the striatum seen on quantitative MRI scans in patients with TS.²² The left putamen is usually larger than the right in right-handed subjects. Singer et al have shown that the right putamen is larger in one-third of TS patients. The putamen is linked to the supplementary motor cortex, which is the primary site of motor planning. The tics may arise from the putamen and the urges from the supplementary motor cortex and anterior cingulate. The OCD and affective change

could arise from abnormal activity in the caudate. Attentional disturbance may be related to cingulate-basal ganglia-parietal circuit dysfunction.

Detection of Psychogenic Movement Disorders

It is well known that stress exacerbates movement disorders. However, not all problems of involuntary movement reflect a neurogenic etiology. Occasionally, the abnormal movements are caused entirely by psychogenic factors. These cases can be quite dramatic and the patient and family may insist that a neurological diagnosis be made. Most commonly, psychogenic movement disorders are driven by unconscious forces and are categorized as a conversion disorder. Differentiating neurogenic from psychogenic cases can be difficult.

The most common psychogenic gait disturbance is astasia-abasia. When separately tested, the patient demonstrates good strength, balance and coordination. The gait, however, is markedly abnormal. Patients lose balance without warning and seem in great danger of falling. They right themselves by grabbing onto objects and people in the room and rarely fall.

Virtually all movement disorders can be mimicked and are therefore susceptible to imitation.

Virtually all movement disorders can be mimicked and are therefore susceptible to imitation. Koller et al reviewed 24 patients with psychogenic tremor,²³ and Monday and Jankovic recently described a series of patients with psychogenic myoclonus.²⁴ Whole body rigidity with opisthotonic posturing and asymmetrical thrashing are two common types of abnormal movement patterns seen in psychogenic epilepsy. There is a high incidence of childhood physical and sexual abuse in patients with psychogenic epilepsy. The incidence of early abuse has not been documented in patients with psychogenic movement disorders.

The clinician should try to discern: 1) do the movements fit the pattern of a

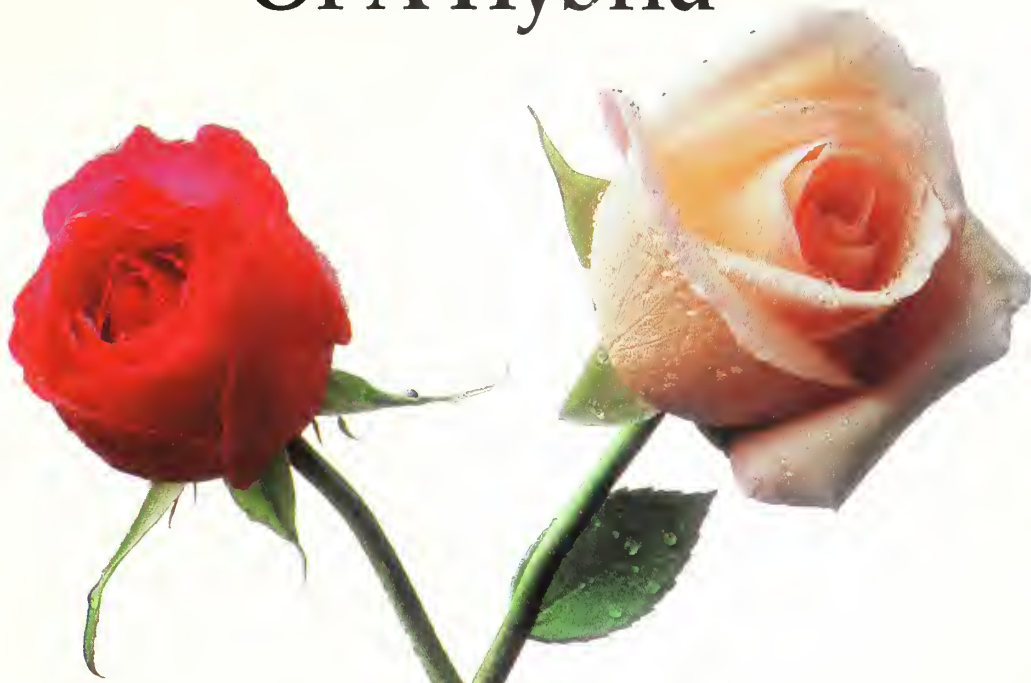
known syndrome; 2) are there other inconsistencies in the exam such as give-away weakness or inconsistent sensory loss; and 3) is there evidence of considerable stress or underlying psychopathology. Often these patients are not obviously emotionally disturbed and identifying underlying psychopathology may require considerable expert probing. It is important to communicate the diagnosis of psychogenic movement disorder to the patient and their family so that a prolonged diagnostic evaluation can be avoided, unnecessary medications discontinued, and appropriate psychiatric treatment instituted.

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CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: General: *Enalapril Maleate, Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.1 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided. (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium: Enalapril should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Enalapril Maleate and Hydrochlorothiazide).

Pregnancy: *Enalapril Hydrochloride:* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses, 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*, below.) *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality:* ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely, (probably less often than once in every thousand pregnancies) no

10 mg



25 mg

alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. (Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.)

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide, Teratology Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4-5 mg/kg/day (approximately 1-2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Neonatology Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: General: *Enalapril Maleate, Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions*.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgical Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscle fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hyperkalemia may develop, especially with brisk diuretics, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hyperkalemia. Hyperkalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Inhibiting Renin/Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the

treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hypoglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postmy-

pathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magne-

sium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients, Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions, Enalapril Maleate, Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See *WARNINGS*.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methylglucosides, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium. Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics:—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin):—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs:—additive effect or potentiation.

Cholestyramine and colestipol resins:—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH:—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine):—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine):—possible increased responsiveness to the muscle relaxant.

Lithium:—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs:—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse

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bone marrow assay

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively (150 and 300 times the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: reverse-mutation assay with *S. typhimurium*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 800 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (chromogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy, Prenatal/Postnatal Development: (First trimester) and (Second and third trimesters) See WARNINGS.

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Adverse Reactions: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain, *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia, *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth, *Neurological:* Insomnia, nervousness, paresthesia, somnolence, vertigo, *Skin:* Pruritus, rash, *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, Cough.

Clinical Laboratory Test Findings, Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC, but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Other adverse reactions that have been reported with the individual components are listed below, and, within each category, are in order of decreasing severity.

Enalapril Maleate: Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, Hemodynamic/Patient's), *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS), pulmonary embolism and infarction, pulmonary edema, rhythm disturbances including atrial tachycardia and bradycardia, atrial fibrillation, hypotension, angina pectoris, *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic pattern), melena, anorexia, glossitis, stomatitis, dry mouth, *Hematology:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported, a causal relationship to enalapril has not been established. *Nervous System/Synthetic:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia), *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecostasis, *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity, *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide: *Body As A Whole:* Weakness, *Digestive:* Pancreatitis, jaundice (intrahepatic, cholestatic, jaundice), sialadenitis, cramping, gastric irritation, anorexia, *Hematology:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia, *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions, *Musculoskeletal:* Muscle spasm, *Nervous System/Synthetic:* Restlessness, *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS), *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia, *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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YOCON® YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

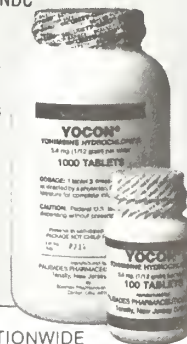
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

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Drug-Induced Movement Disorders

Stuart S. Rich, MD

Just because a patient with a movement disorder has been on neuroleptics does not mean that the movement disorder is inevitably tardive dyskinesia.

Movement disorders include hypokinetic disorders (various forms of parkinsonism), hyperkinetic disorders (Huntington's chorea, tardive dyskinesia, etc.), and dystonias. Drug-induced hypokinetic movement disorders generally are caused by blocking dopamine transmission, while hyperkinetic movement disorders are caused by drugs that enhance dopamine stimulation, either acutely or chronically. Dystonias can appear with either acute or chronic administration of dopamine antagonists. This review will emphasize the most common movement disorders that are induced by dopamine antagonists: acute dystonia, akathisia, drug-induced parkinsonism (DIP), and tardive dyskinesia (TD).

Interest in drug-induced movement disorders is not limited to psychiatrists and neurologists. All physicians who treat patients will create drug-induced movement disorders inadvertently and will have the opportunity to treat patients with drug-induced movement disorders. Dopamine receptor-blocking drugs, including the antipsychotics (neuroleptics), antiemetics, and the gastrointestinal motility enhancer metoclopramide, are among the most commonly prescribed medications (Table 1). Neuroleptics are used mainly to treat psychosis but are prescribed, often inappropriately, to treat agitated behavior in demented or mentally retarded patients, who are particularly susceptible to neuroleptic side-effects. Both neuroleptics and nonpsychiatric drugs that are dopamine receptor blockers are associated with the same movement disorders. Clinicians are often less vigilant in looking for associated drug-induced movement disorders when prescribing nonpsychiatric medications.

A Clinical Vignette

A psychiatrist was asked by a neurosurgery service to evaluate a patient for

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Table 1.—Drugs That Cause Parkinsonism

Drug	Indication	Mechanism
All antipsychotics (except clozapine)	Treatment of psychosis and agitated behavior	D ₂ receptor blockade
Metoclopramide (Reglan)	Gastroparesis	D ₂ receptor blockade
Prochlorperazine (Compazine)	Antiemetic	D ₂ receptor blockade
Droperidol (Inapsine)	Antiemetic	D ₂ receptor blockade
Methyldopa (Aldomet)	Hypertension	Competitive inhibition of dopa decarboxylase, an enzyme necessary for the conversion of dopa to dopamine, plus formation of a false neurotransmitter that may compete with DA for receptors in the striatum.
Rauwolfia alkaloids, eg, reserpine	Hypertension, psychosis	Presynaptic depletion of dopamine
Tetrabenazine	Hyperkinetic movement disorders	Presynaptic depletion of dopamine
Amoxapine	Depression	D ₂ receptor blockade

suspected depression and to make recommendations for antidepressant treatment. On examination, the patient exhibited a "flat affect" but was neither sad nor anhedonic, and was bradykinetic, rigid, and had a slow resting tremor. The patient had no past psychiatric history, had never been treated with antipsychotics, but had recently been put on metoclopramide for gastrointestinal symptoms. Upon discontinuation of the drug, her symptoms gradually resolved.

Neuroleptic-Induced Movement Disorders

Basic Properties of Neuroleptic Drugs

"Typical" neuroleptic drugs (ie, all those currently on the market except clozapine) are essentially equivalent in antipsychotic efficacy but come with a spectrum of side-effects. The neuroleptics can be ranked by potency of antipsychotic effect, which correlates with potency of D₂ receptor antagonism. High-potency neuroleptics, such as haloperidol and fluphenazine, are most likely to

cause extrapyramidal side-effects, but are less sedating, have less anticholinergic side-effects and cause less orthostatic hypotension than low-potency neuroleptics such as chlorpromazine or thioridazine, which have side-effect profiles that are the inverse of the high-potency neuroleptics. Neuroleptics of intermediate potency such as perphenazine or loxapine have intermediate side-effect profiles.

Acute Dystonic Reactions

Clinical features.—Acute dystonic reactions usually occur within the first

ABBREVIATIONS USED

AIMS: Abnormal Involuntary Movement Scale
DA: Dopamine
DIP: Drug-induced parkinsonism
ECT: Electroconvulsive therapy
GABA: Gamma amino butyric acid
PD: Parkinson's disease
SNC: Substantia nigra
TD: Tardive dyskinesia

few hours following exposure to neuroleptics, though later onset may occur, usually following an increase in the dose or a switch to a more potent agent. According to Ayd,¹ 50% of such reactions occur within 48 hours, and 90% occur within 5 days of initiation of neuroleptic therapy.

Acute dystonic reactions are sustained or at times intermittent involuntary contraction of muscles resulting in an array of abnormal movements and postures. Commonly these consist of oculogyric crises, torticollis, retrocollis, trismus, forced jaw opening, grimacing, blepharospasm, and glosso-pharyngeal contractions. These latter may result in dysarthria, dysphagia, or respiratory stridor.² Children tend to display more axial dystonias.

Acute dystonic reactions are generally painful and frightening to the patient and should be treated promptly (see below).

Epidemiology.—The overall incidence of acute dystonic reactions is approximately 2.5% to 5%.²

Risk factors.—High-potency neuroleptics such as haloperidol appear to carry the highest risk for acute dystonic reactions. The lower risk for acute dystonic reactions of the low-potency neuroleptics has been attributed to the prophylactic action of the anticholinergic properties of the low-potency neuroleptics. Young age, male sex, and a history of previous episodes of acute dystonia are additional risk factors for acute dystonic reactions. Moderate to high doses are more likely to result in acute dystonic reactions than low doses, or, interestingly, extremely high doses (in the range of 2000 chlorpromazine equivalents per day).³

Treatment.—Acute dystonic reactions respond rapidly to benztropine 2 mg or diphenhydramine 50 mg. These drugs are commonly administered intramuscularly, but they should be administered intravenously, since the response with this method is considerably more rapid, a point worth noting as the symptoms are usually of great distress to the patient. Acute treatment should be followed up with standing oral doses of anticholinergics for at least a week and then cautiously tapered.

Prophylaxis.—The decision whether to institute prophylactic treatment with anticholinergics or diphenhydramine along with the initial dose of neuroleptic depends upon an assessment of the degree of risk of an acute dystonic reaction as well as the likelihood of harm. This

Table 2.—Common Pitfalls with neuroleptic-induced movement disorders

Pitfalls	Pointers
Confusing TD and DIP.	(1) Look for rhythmic alternating movements of tremor vs. random, jerky chorea of TD. (2) A sufficient decrease in the dose of the neuroleptic should improve DIP and cause a transient exacerbation of TD within a week or so.
Treating TD with anticholinergics (there is an unfortunate tendency on the part of some clinicians to treat <i>all</i> movement disorders in patients on neuroleptics with anticholinergics).	Although anticholinergics improve DIP, they usually make TD worse.
Failing to detect mild DIP.	(1) Examine the patient for signs, of akinesia, eg, decreased blink rate, decreased associated movements while walking, and decreased facial expression. (2) Use reinforcing maneuvers when examining patient for rigidity. (3) Look for rigidity of axial muscles in the neck by moving the patient's head.
Assuming that only antipsychotic medications cause dystonic reactions, DIP, TD, and akathisia.	Remember that some commonly used drugs, eg, Reglan and Compazine that are not antipsychotics may cause the same problems (see Table 1).
Mistaking mild DIP for depression.	If the patient is neither sad nor anhedonic, and has rigidity and a resting tremor, remove the offending agent, rather than treating a nonexistent depression with an antidepressant.
Relying on the presence of "cogwheeling" to diagnose DIP.	Rigidity may be present without cogwheeling.
Concluding from the presence of an orofacial dyskinesia that the patient has schizophrenia.	Not all such dyskinesias are TD. Not only is there a danger of misdiagnosis of the dyskinesia itself but this spurious reasoning can lead to the impaired mental status of a delirious patient being attributed to a nonexistent psychiatric disorder.
Mistaking the "rabbit syndrome" for TD because of its location.	This syndrome is merely a parkinsonian tremor of the perioral region and close inspection should reveal whether the patient has rhythmic or choreiform movements.

must be balanced by the known side-effects of anticholinergic drugs. Thus, when administering a moderate to high dose of a high-potency neuroleptic to a paranoid young male who is unenthusiastic about the intervention in the first place, the usual practice is to co-administer a prophylactic agent.

Acute Akathisia

Clinical description.—Akathisia is a

common and underdiagnosed complication of neuroleptic treatment. It consists of a subjective feeling of restlessness in which the patient feels an urge to move to relieve a sense of discomfort. Patients are typically observed to frequently shift position while sitting in a chair, to cross and uncross their legs, and to pace. An especially implicative sign is marching in place.

Differential diagnosis.—Chore-

oathetotic movement disorders may be confused with akathisia as can worsening psychosis. Choreaethetosis is a bona fide involuntary movement disorder, whereas movements of akathisia are voluntary movements in response to a subjective drive to move.⁴ When the mental state of the patient is such that he cannot communicate reliably, this can be a difficult distinction to make. Similarly, distinguishing akathisia from increased psychosis in a patient whose mental state is impaired poses a difficult problem. A common error is to interpret akathisia as increased anxiety or psychosis, and therefore to increase the neuroleptic dose which, of course, only makes matters worse. Akathisia should be considered when patients worsen on neuroleptics.

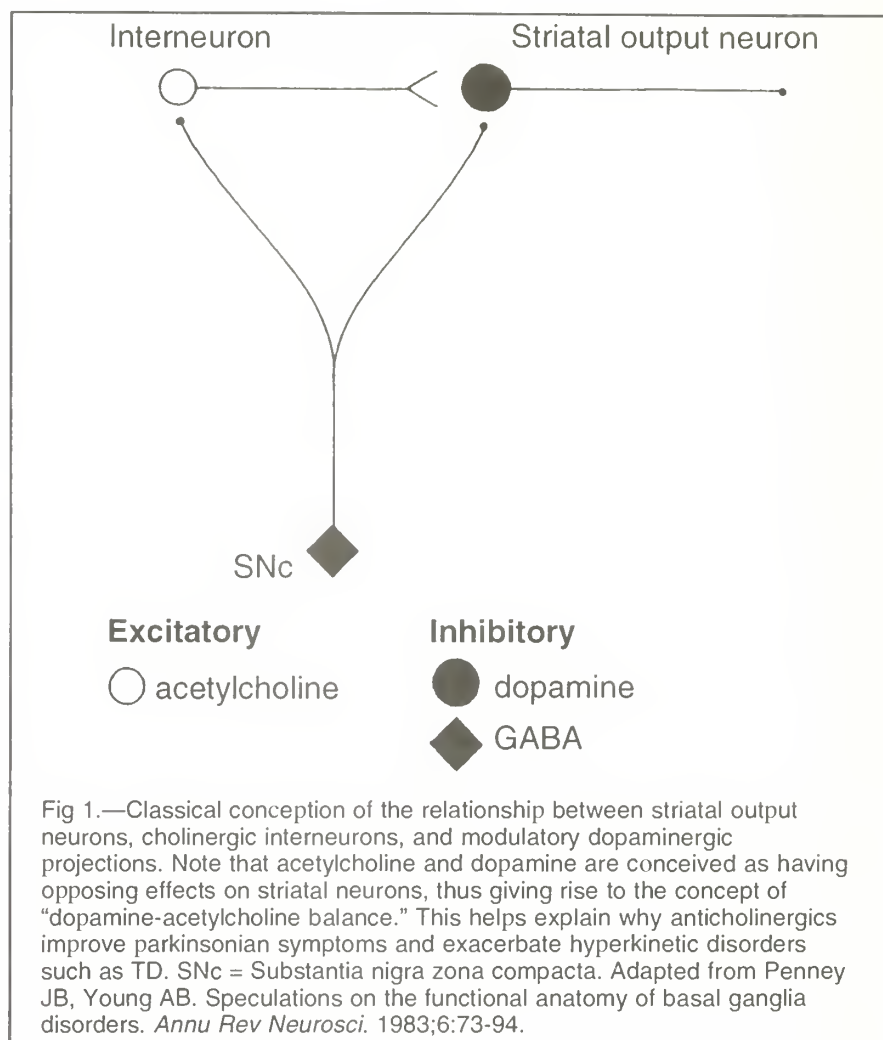
Restless legs syndrome shares many of the features of akathisia, but is distinguished by discomfort being limited entirely to the legs, the absence of subjective restlessness, predominance of symptoms in the evening, and restriction of the symptoms to when the patient is reclining.⁴ A history of neuroleptic exposure usually suffices to make the diagnosis of akathisia since restless legs syndrome is not, in general, drug-induced.

Treatment.—The first line treatment for akathisia is reduction of the neuroleptic dose if this is feasible. Anticholinergics, amantadine, and benzodiazepines all probably have some efficacy for akathisia in many patients, but the first line pharmacologic treatment for akathisia is beta blockers. Antiparkinsonian medication seems to be most efficacious for akathisia in the presence of concomitant DIP.⁵ Propranolol 10 mg to 20 mg tid usually suffices when DIP is not present.

Drug-Induced Parkinsonism

Phenomenology and diagnosis.—Drug-induced Parkinsonism (DIP) is phenomenologically indistinguishable from Parkinson's disease (PD) and shares its heterogeneity of presentation. Thus the four cardinal features of PD, tremor at rest, bradykinesia, rigidity, and postural instability are also the hallmarks of DIP. The distribution of parkinsonian signs in populations of patients with DIP, however, probably differs from that of PD.⁶

Differential diagnosis.—The most common entity from which DIP needs to be distinguished is PD and other forms of parkinsonism. Putative distinguishing features include a history of neuroleptic exposure in DIP as opposed to PD, a chronically progressive course in PD as opposed to a course that stabilizes after a



few months in DIP, and the predominance of PD as a disease of the elderly.⁷ While it has often been claimed that DIP can be distinguished from PD by the symmetric distribution of symptoms at onset of DIP in contrast to the commonly asymmetric distribution of symptoms at onset,⁷ such is not the case; DIP often does present with asymmetric involvement.^{6,8} Mild cases of DIP can sometimes be mistaken for depression as in the clinical vignette above.

Pathophysiology.—The similarity between the phenomenology of DIP and PD can be accounted for by their known pathophysiology. PD is a disease of degeneration of dopaminergic cells in the midbrain that project to the striatum, resulting in a profound deficiency of dopamine in the striatum. DIP is caused by blockade by neuroleptics of dopamine D₂ receptors on striatal cells, resulting in a functional deficiency of dopamine in the striatum. Parkinsonism can also be induced by drugs that deplete presynaptic dopamine such as reserpine, tetra- benazine, and alpha-methyltyrosine. Thus, the pathophysiology of the two

disorders is quite distinct, but it is readily apparent why their functional consequences should be so similar.

The classic model of striatal circuits,⁹ though now known to be greatly oversimplified and to some extent inaccurate, retains considerable clinical heuristic value. In this model, dopaminergic projections to the striatum are inhibitory at both striatal output neurons and at cholinergic interneurons, which, in turn, make excitatory synaptic contact with the striatal output neurons (Figure 1). Thus arises the concept of “dopamine-acetylcholine balance,” wherein changes in one of these neurotransmitters can counteract a similar change in the other. In particular, this model explicates the efficacy of anticholinergic drugs in the treatment of parkinsonism, as well as their exacerbation of hyperkinetic movement disorders.

Epidemiology.—Estimates of the incidence of DIP have varied widely, depending on the population studied and the sensitivity of the examination. In psychiatric populations, moderate to severe DIP occurs approximately in 10% to

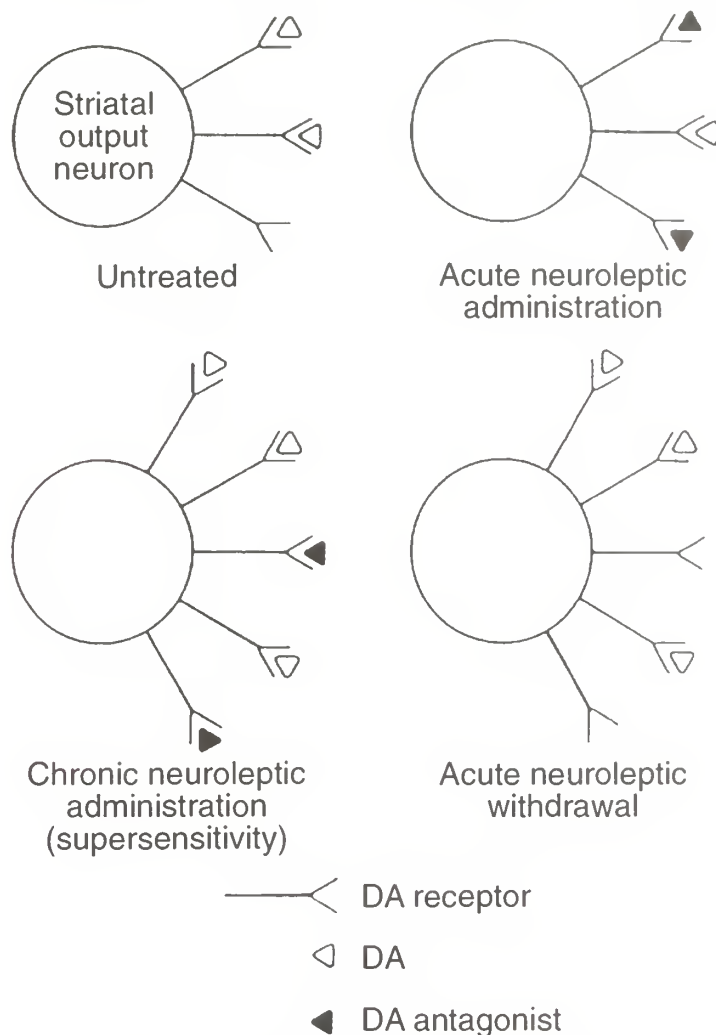


Fig 2.—The dopamine supersensitivity hypothesis of TD states that chronic administration of dopamine (DA) receptor antagonists results in a “denervation supersensitivity” or up-regulation of dopamine receptors. This explicates the development of a hyperkinetic movement disorder (TD) after chronic administration of neuroleptics, the suppression of TD by increasing neuroleptic dosage, and the “unmasking” of TD by lowering neuroleptic dosage.¹⁷

15% of patients exposed to neuroleptics,² but if very mild cases are counted, the vast majority of patients develop DIP to some degree.¹⁰ Risk factors for DIP include female sex (2:1 ratio), increased age, greater neuroleptic potency, and higher neuroleptic dose. Also, there are reports that concomitant therapy with fluoxetine can exacerbate DIP. The known risk factors cannot account entirely for the pattern of DIP, however, and there is considerable unexplained individual variability.

Treatment.—Most cases of neuroleptic-induced parkinsonism are mild, often not even noticed by the patient, and often spontaneously remit within 3 months even with continuation of the neuroleptic. For patients with significant

symptoms, lowering the dose of the neuroleptic or switching to a lower potency neuroleptic will often alleviate the problem, as will discontinuation of the neuroleptic, if this is possible. DIP may persist for more than 18 months, even after discontinuation of the neuroleptic, and the patient must be warned of this. If the patient improves at first, and then worsens, the diagnosis of PD must be entertained.

Pharmacologic treatment of DIP usually consists of an anticholinergic such as bethtropine (Cogentin) 0.5 mg to 2 mg bid or amantadine (Symmetrel) 100 mg bid, which is believed to work by enhancing dopamine release. These agents have roughly equivalent efficacy in general, but one may be more effective than the

other for a given individual and they have different side effect profiles. Anticholinergics are more likely to exacerbate dementia and do so commonly, while amantadine is more likely to exacerbate psychosis, but does so uncommonly. In either case, an attempt to taper the antiparkinsonian drug after a few months should be made.

L-dopa and dopamine agonists are rarely used to treat DIP because of the risk of exacerbating psychosis and the uncertain benefit of attempting to stimulate blocked dopamine receptors.

Patients who are truly intolerant of the extrapyramidal side effects of neuroleptics (eg, a patient with concomitant PD) can be switched to clozapine, an atypical antipsychotic that does not cause DIP or TD, but which may cause agranulocytosis, requiring weekly blood count monitoring.

Electroconvulsive therapy (ECT) is another option for patients with DIP refractory to the usual treatment, because of its efficacy in both psychosis and in parkinsonism, but the benefits in parkinsonism last only days to weeks.

There is disagreement over whether prophylactic antiparkinsonian treatment should be instituted when neuroleptic treatment is initiated. My practice is to use prophylactic treatment only in acutely psychotic patients who are likely to become noncompliant if they experience side effects. If prophylactic treatment is employed, the antiparkinsonian agent should be tapered on a trial basis after the patient is stabilized.

Tardive Dyskinesia

Clinical description.—Tardive dyskinesia is a syndrome of abnormal involuntary movements resulting from prolonged neuroleptic exposure. The syndrome may arise either during or following the cessation of long-term neuroleptic therapy. Raising the dose of neuroleptic suppresses the movement disorder acutely, while lowering the dose results in an exacerbation of the movements acutely.

Tardive dyskinesia is notorious for manifesting itself by oral buccal dyskinesic movements including chewing movements, protrusion of the tongue, lip smacking, puckering, and pursing of the lips, but it can consist of any hyperkinetic movement disorder of any part of the body, including choreiform movements of the hands and feet, axial symptoms of pelvic thrusting, or even dyskinesias of breathing and swallowing.¹¹

Epidemiology and risk factors.—

The incidence of tardive dyskinesia is probably 3% to 4% per year of exposure to neuroleptics. It is unusual for tardive dyskinesia to develop before at least 3 months of exposure to neuroleptics.

For obvious reasons, much attention has been devoted to determining whether different antipsychotics ought to be regarded as more or less culpable than others in causing drug-induced movement disorders such as tardive dyskinesia. In particular, thioridazine has gained a possibly undeserved reputation as being more innocent in this regard, relative to higher potency agents such as haloperidol.¹²

The standard of practice is to assume that the risk of developing TD is proportional to the dose of the drug, the duration of exposure, and ultimately the cumulative dose of the drug. This view obligates the clinician to minimize the exposure of the patient to neuroleptics, although the evidence for a correlation between the risk of TD and various measures of the magnitude of exposure is mixed.¹² The frequency and severity of TD increases with age and occurs more often in women than in men (ratio 1.68:1).¹¹

Natural History.—Most cases of tardive dyskinesia are mild, though there is a minority of patients who develop severe and disabling tardive dyskinesia. Tardive dyskinesia does not always progress in severity, and some patients improve even with continued neuroleptic treatment. Nevertheless, the standard of practice is to lower the dosage of neuroleptic or discontinue it, if possible, when tardive dyskinesia appears. In chronic schizophrenia, the risks of neuroleptic discontinuation very often outweigh the risks of continuation. Most patients are not troubled by the symptoms, although they may be cosmetically embarrassing. Often, for example, patients with abnormal oral-buccal movements will simply chew gum to make the movements appear more natural. Usually the symptoms gradually improve and often disappear after discontinuation of the neuroleptic. Occasional cases of tardive dyskinesia are severe, however, and some are permanent. Therefore, the risks and benefits must always be carefully weighed when prescribing long-term neuroleptics and fully informed consent must always be obtained. Every patient who is prescribed a neuroleptic should have a formal examination for TD, such as the AIMS scale, before initiation of the neuroleptic and every 3 months thereafter that the patient remains on the drug.

Pathophysiology.—

There is considerable heuristic value in the much maligned, however deservedly, dopamine supersensitivity hypothesis of tardive dyskinesia (Figure 2). This hypothesis states that the hyperkinetic movements of TD result from a supersensitivity of the dopamine receptor population in the striatum that is due to chronic dopamine receptor blockade. It is useful, for example, in thinking about why tardive dyskinesia improves acutely after increases in dosage of neuroleptics, and why it is transiently exacerbated by withdrawal of neuroleptics. The dopamine-acetylcholine balance theory (Figure 1) explicates why anticholinergic drugs exacerbate tardive dyskinesia that is improved by cholinergic drugs. The GABA hypothesis of tardive dyskinesia¹³ explains some of the preclinical subtleties of tardive dyskinesia better than the older hypothesis but is not as yet more clinically useful.

Management.—*Weighting of Risks and Benefits.*—In a typical case, a schizophrenic patient will develop mild tardive dyskinesia, which he will prefer to the suffering he experiences from his psychotic symptoms. An all too common scenario, however, is that antipsychotics are prescribed for nonspecific symptoms of agitation or behavioral dyscontrol in the demented elderly or the mentally retarded, both of whom are especially susceptible to developing tardive dyskinesia in its more severe forms, and this unfortunate practice is often embarked upon without appropriate trials of alternative agents to treat aggressive behavior.¹⁴

Pharmacologic Therapy.—There is no consistently beneficial pharmacologic therapy for TD, in spite of investigations of many drugs aimed at the dopaminergic, cholinergic, and GABAergic systems.

Suppression of TD with higher doses

of neuroleptics makes one apprehensive that, though it may abolish symptoms in the short run, it may lead to an exacerbated case of TD with greater disability and even more refractory to treatment. Nevertheless, it is becoming clear that many cases of TD do not progress in spite of continued neuroleptic treatment, and in cases where respiration or nutrition are compromised, suppression of the TD with neuroleptics may be the most viable approach.

Treatment with the presynaptic dopamine depleters reserpine and tetraabenazine has met with fair success. Occasional patients benefit from treatment with benzodiazepines, baclofen, valproic acid, or calcium channel blockers.

Treatment of DIP in the patient with coexisting TD is problematic and often unsuccessful because the treatments for one tend to make the other worse. A subset of these patients tolerate anticholinergic treatment well, however, so it should be tried. For some of these patients, clozapine or ECT may be an option since both sometimes improve TD as well as DIP.

Differential diagnosis and evaluation.—Psychiatrists have a saying along the lines of, "Just because you're paranoid doesn't mean they're not out to get you." Just because a patient with a movement disorder has been on neuroleptics does not mean that the movement disorder is inevitably TD; other movement disorders must be considered. The differential diagnosis of TD and the appropriate evaluation has recently been well reviewed in detail.¹⁵ Common issues follow.

A patient with Huntington's or Wilson's disease may have been on neuroleptics for psychotic symptoms that predated their primary movement disorder. Nevertheless, there is the possibility that the primary movement disorder may be

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complicated by supervening TD. These alternative diagnoses, however, are quite uncommon.

A mild, acute parkinsonian tremor sometimes may be mistaken for mild choreiform TD and vice versa. Prolonged, careful observation usually reveals whether the movement is a rhythmic tremor or a random, jerky chorea. If not, lowering the dose of the neuroleptic should improve a tremor and exacerbate TD.

A subtype of DIP is the so-called "rabbit syndrome," which is simply a parkinsonian tremor of the lips and perioral region. A common error is to confuse this syndrome with tardive dyskinesia because of its location.^{6,10}

Spontaneous Movement Disorders.—Three kinds of spontaneously occurring non-drug-induced movement disorders can be confused with TD. About 8% of the normal elderly develop idiopathic orofacial dyskinesias similar to TD, especially if they are edentulous or have ill-fitting dentures. There is considerable evidence that untreated schizophrenics develop (or, rather, developed since there are virtually no chronic schizophrenics left that have not been treated with neuroleptics) a syndrome phenom-

enologically identical to TD, albeit at a lower rate. Perhaps this is not unrelated to the observation of nonprogressive TD. Finally, both schizophrenics and the mentally retarded exhibit mannerisms that can be confused with TD. They differ from the movements of TD in being more complex and repetitive.

Tardive dystonia.—Tardive dystonia is a less common drug-induced movement disorder resulting from prolonged exposure to neuroleptics than tardive dyskinesia, but it tends to be more disabling. The symptoms include the development of dystonic movements following prolonged neuroleptic exposure, primarily involving the face and neck and especially producing retrocollis.¹² Estimates of the prevalence in psychiatric patients vary widely between 1.5% and 21%.¹²

Tardive dystonia differs from tardive dyskinesia not only in being more disabling, but in being less likely to remit.¹²

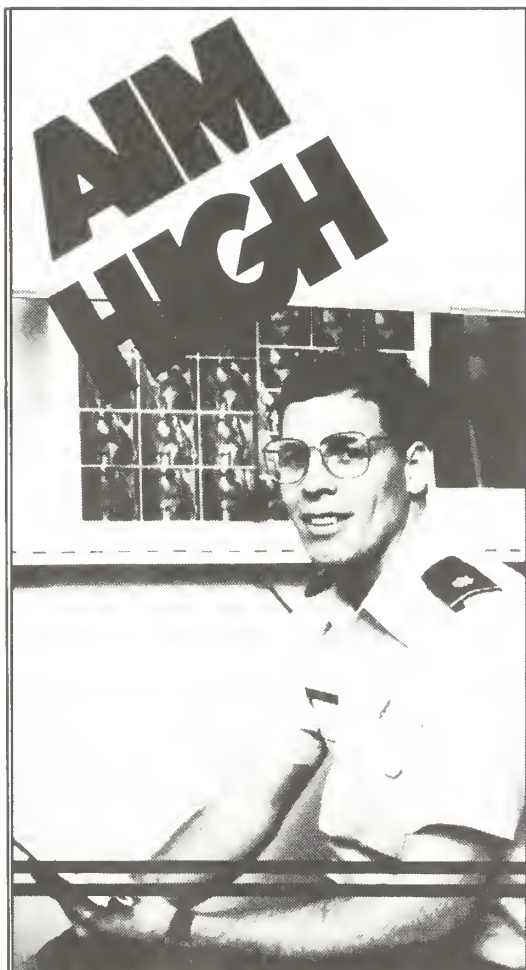
Tardive akathisia.—Tardive akathisia has become recognized increasingly in recent years as a complication of neuroleptic treatment. Tardive akathisia is generally associated with TD⁴ and often responds well to treatment with dopam-

ine depleting agents such as reserpine and tetrabenazine.¹⁶

Other tardive movement disorders.—Other tardive syndromes that are due to neuroleptic exposure, namely tardive Gilles de la Tourette's syndrome, tardive myoclonus, and tardive tremor have been described but are rare and not well studied.¹²

Conclusion

Drug-induced movement disorders are common and have the potential for causing considerable disability. The adverse consequences of these syndromes can be minimized by vigilant clinicians who systematically examine patients at risk for these disorders and who manage them properly when discovered. The best management is, of course, prevention, which starts with the judicious prescription of neuroleptics, and an awareness of the potential for certain nonpsychiatric medications to cause the same movement disorders. In particular, there is currently an epidemic of movement disorders in this country among the demented and the developmentally disabled populations caused by prescription of neuroleptics for nonspecific (ie, not related to psycho-



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sis per se) behavioral problems, many of which could be managed otherwise.

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Essential Tremor

Samuel A. Elias, MD, PhD

Some useful features differentiate essential tremor (ET) from parkinsonian tremor: ET is not decreased with dopamine agonists; bradykinesia, rigidity and postural instability are absent; and there may be complex tremors but the characteristic pill-rolling tremor of parkinsonism is not seen.

Tremor is a somewhat regular, rhythmic oscillation of part of the body. Its rhythmic quality helps distinguish it from other forms of involuntary movements such as chorea, ballismus, tics, dystonia, and myoclonus. Of these only myoclonus may occur as a rhythmic disturbance; the others are either random or sustained. Myoclonus produces a lightning-like muscle jerk that is considerably more abrupt than a tremor. If the myoclonus is rhythmic, it can usually be distinguished from tremor by its appearance on electromyographic testing. Although tremor usually involves the hands, it may occur in the tongue, jaw, facial muscles, or feet.

Several behavioral criteria are useful in the classification and treatment of tremor. An *action* tremor occurs during motion or muscular exertion. A *postural* tremor occurs in a limb during a maintained posture against gravity. An *intention* tremor accentuates near the end point of the motion; for example, near one of the end points of the finger-nose-finger test. If the tremor accentuates when the limb is "at rest", it is called a *rest* tremor, which is probably a misnomer, since some minimal activation may be necessary to produce a rest tremor (eg, a Parkinsonian rest tremor may abate when the limb is fully supported and the patient is very relaxed). For unknown reasons all tremors resolve during sleep.

(Benign) Essential Tremor

The term "benign essential tremor" is somewhat misleading since significant disability may occur. Fortunately, this is rare. Eating food and drinking from a glass without spilling can become in-

creasingly difficult. Writing may become impossible. Careers in occupations requiring fine manual dexterity or public speaking may be prematurely ended. Thus, although most essential tremor is so mild that people don't know they have it, it may produce social embarrassment, and the quality of life can be reduced.

Essential tremor may affect the voice, face, neck, trunk or limbs. The tremor is not known to affect the eyes, and it only rarely affects the legs. Occasionally it may be seen in the lips, chin, tongue, or trunk. Essential tremor is usually postural and is accentuated by voluntary movement. It may appear as a resting tremor in very advanced cases.

In the US, essential tremor is the most frequent movement disorder in adults, occurring in 4 to 60 per 1000 people.¹ It can occur at any age from childhood, but its prevalence is higher in patients over 40 years old. About 50% of cases have a family history of tremor. These families exhibit a Mendelian autosomal dominant pattern of inheritance² and are often said to have *familial* tremor. When ET developed in old age it had been called *senile* tremor, a term no longer used.

Clinical Presentation

History

Typically, the patient is elderly, and seeks medical attention only after the tremor has been present and gradually worsening for several months. The patient may complain of specific functional disabilities or may report social embarrassment due to the tremor. For some patients, public speaking, writing, shaving, holding a cup of liquid, or fastening a button are virtually impossible. The tremor may lead to gradual social withdrawal. Not infrequently, the patient will spontaneously state that a few ounces of alcohol will substantially reduce the tremor amplitude. Cold, hunger, fatigue, sym-

pathomimetics, and anxiety may all cause increase tremor. Contrary to anecdotal reports, nicotine³ and caffeine⁴ had no demonstrable effects in controlled studies. The patient with pure ET does not complain of muscle pain and stiffness, slowness of movement (bradykinesia), or decreased frequency of movement (hypokinesia). However, it is important to recognize that ET may co-exist with Parkinsonism or other conditions and may need to be treated independently.

On Examination

Mental status, cranial nerves, sensation, muscle strength, and deep tendon reflexes are all normal. The voice may be tremulous, but there is no dysarthria. There is no evidence of the strained voice of spastic dysphonia. There are no involuntary rhythmic movements of the palate or uvula. If a head tremor is present, it is a postural tremor (ie, it disappears when the head and neck are fully supported and the patient is relaxed and reclining). The major component of the head tremor may involve neck flexion and extension (a "yes-yes" tremor) or involve lateral rotations of the head (a "no-no" tremor). These two forms may also alternate. In isolated ET, there is no pill-rolling tremor of the fingers. There is no evidence of bradykinesia or hypokinesia. There are no unusual postures (dystonias) while sitting, standing, or completely relaxed and distracted. However, when patients write, they may grip the pen so firmly to suppress the tremor that cramp develops, making the distinction between writer's cramp and tremor difficult. Muscle tone is normal except there may be cogwheel

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ABBREVIATIONS USED

BOTOX: Botulinum toxin
EMG: Electromyogram
ET: Essential tremor
PD: Parkinson's disease

ing. This is nothing more than a superimposed tremor upon a passive movement.

Special provocative maneuvers may enhance essential tremor.

Provocative Maneuvers

Holding a pen or a cup filled with water in the outstretched hand may accentuate the tremor. Writing may increase the tremor amplitude (Figure 1). Drawing an Archimedes spiral while the hand and arm are unsupported will usually make the tremor much worse. (See Figure 2.⁵) Certain postures may enhance a tremor. For example, tremor may worsen with the arms folded across the chest, or held in front of the body mildly pronated.

Tremor Frequency

ET exhibits frequencies ranging from 4 to 12 Hz.^{6,7} Since this frequency range overlaps that of enhanced physiological tremor and various pathological tremors it is *not* particularly useful in differentiating this condition from other tremors. The frequency of the tremor obeys an inverse relationship to tremor amplitude.⁷ The tremor amplitude may increase and the tremor frequency may decrease with disease progression and patient age.

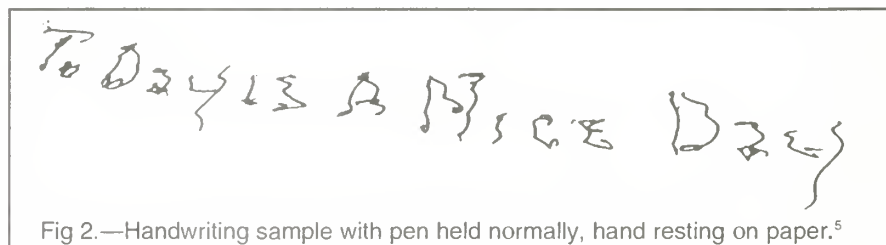
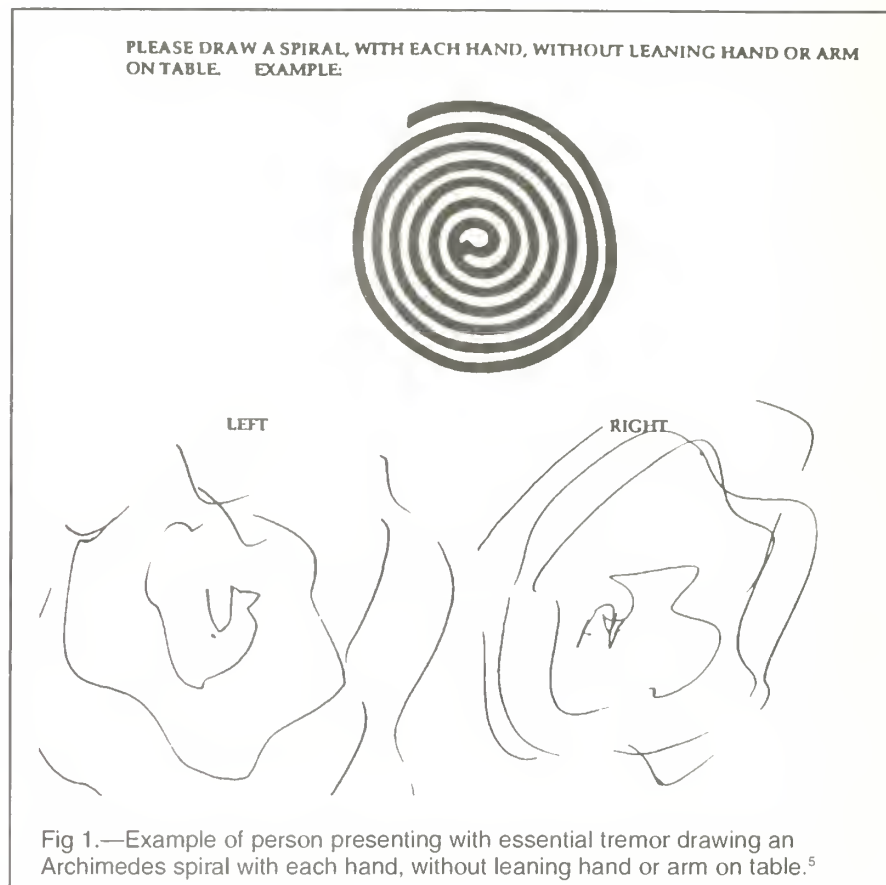
Electro-Diagnostic Features

In ET, when the arm is held in extension against gravity, the bursts of EMG activity in antagonist muscles are usually synchronous⁸ but may be alternating, as in Parkinsonian tremor. Thus a clear distinction between ET and Parkinsonism cannot be made using this criteria alone. It is of some interest, however, that the alternating pattern is seen in ET patients who have the larger amplitude and lower frequency tremors. Many of the patients with the alternating pattern are less responsive to propranolol^{9,10} and more responsive to primidone.

Diagnosis

No definitive diagnostic test nor fixed set of diagnostic criteria exist for essential tremor. The diagnosis may be made by applying the following guidelines:¹¹

1. There is an intermittent or constant tremor of the hands, head or voice.
2. Tremor may be postural or kinetic (it accentuates with movement), and a resting component may be seen in advanced cases.



3. No other neurological abnormalities related to systemic or neurological diseases are present. (Of course, these may be present by chance occurrence.)
4. There is no other medical explanation of the tremor.
5. A positive family history of tremor supports the diagnosis (but its absence is uninformative).
6. The diagnosis is supported if the tremor is reduced by alcoholic beverages (but not excluded by a failure to respond).

Some useful features differentiate ET from parkinsonian tremor: ET is not decreased with dopamine agonists; bradykinesia rigidity and postural instability are absent; and there may be complex tremors but the characteristic pill-rolling tremor of parkinsonism is not seen.

Essential tremor and parkinsonism may be confused by some of their com-

mon features: both may be decreased with propranolol and either may exhibit a resting tremor. In addition, many elderly people develop mild signs of parkinsonism, such as akinesia, stooped posture and bradykinesia simply from normal aging. Thus, the presence of ET in this population can present a major diagnostic uncertainty.

As mentioned above, other common medical explanations of tremor should be excluded. Tremors caused by pharmacologic agents are frequently encountered in clinical practice.¹¹ Neuroleptics may induce parkinsonism with rest tremor. Beta adrenergic drugs used in the treatment of bronchospastic disease can enhance physiological tremor. Lithium can mimic ET by inducing tremors of limbs, head and voice. Rarely, valproate can produce a fine resting, postural or kinetic tremor. Tricyclic antidepressants

infrequently produce a tremor of the upper extremities. Alcohol withdrawal is a well known source of generalized tremor. Caffeine is generally believed to enhance tremor, but quantitative studies have failed to demonstrate that caffeine causes tremor. Theophylline may contribute to increased tremor. Nicotine increases the amplitude of physiologic tremor. Synthroid and thyrotoxicosis increase tremor. The calcium channel blockers can induce or accentuate tremor: nifedipine can enhance physiologic tremor, and flunarizine can induce parkinsonism with tremor. Cardiac antiarrhythmic drugs such as lidocaine, procainamide, and amiodarone can produce tremors.

Medical Therapy

Treatment of ET is usually initiated either with propranolol or primidone. Primidone is the most effective drug for the treatment of essential tremor if one excludes alcohol. It also produces sedative side effects. Propranolol has been shown to be effective in essential tremor.¹² It appears to be helpful in decreasing voice, tongue and head tremors as

For some patients, public speaking, writing, shaving, holding a cup of liquid, or fastening a button are virtually impossible.

well as tremors of the upper extremities. It may not be as effective, however, in the treatment of head tremor.¹³ Propranolol is not often well tolerated by the elderly and should not be used in patients with significant asthma, obstructive pulmonary disease, second or third degree heart block, diabetes, congestive heart failure, or depression. One often tries to initiate therapy with primidone. Typical regimens for treatment are discussed below. It should be noted that tremor rarely resolves entirely on these medications. This is unlike PD where some patients will experience a complete recovery from tremor with levodopa or anticholinergics.

Primidone

Primidone will lower the amplitude of the tremor but not the frequency.¹⁴ Because of its sedative effects, it must be started at a low dose and gradually increased. Patients are usually started on a half tablet of 50 mg at night for 3 to 5 days. Once tolerated, it may be increased

slowly to 125 mg at night. If necessary, it may be increased to 250 mg at night. This is in contrast to the usual antiepileptic dosage which is 250 mg 3 times daily. In one study, no increased efficacy was seen above this dose range, and no correlation was found between drug efficacy and serum level.¹⁴ Sedation, nausea and dizziness are common side effects of this treatment, especially in the elderly.

Patients who do not respond adequately to primidone may switch to propranolol or add it to the current regimen.

Propranolol

Propranolol may decrease the amplitude of essential tremor. Like primidone and other drugs, including alcohol, it does not decrease the tremor frequency. The clinical response to propranolol is variable with 50% to 70% of patients exhibiting some symptomatic relief but dramatic relief occurring in a much smaller percentage.¹⁵ The upper limit of the optimal dose range has been found to be 320 mg of propranolol per day, and no correlation has been found between the serum level and the efficacy.⁵ A test dose of 20 mg usually is given to verify that the patient will tolerate the drug. Then the patient may be started on propranolol-LA 80 mg in the morning. If necessary, the dose may be increased in 80 mg steps to 240 mg and subsequently to 320 mg.

Benzodiazepines

Benzodiazepines have not been found to be as effective as primidone or propranolol in the treatment of essential tremor. However, alprazolam, a triazolam analog, has been found to be effective in some patients.¹⁶ In addition, clonazepam in doses of 1 to 3 mg per day has proven effective in the treatment of patients with a predominantly kinetic tremor.¹⁷ Part of the benefit from anti-anxiety medications, such as these, may be related to sedation and reduction in anxiety, since anxiety worsens ET.

Calcium Channel Blockers

Calcium channel blockers may be effective in the treatment of ET. A significant reduction in ET was obtained in a double-blind placebo controlled study using flunarizine (10 mg a day).¹⁸ Of the 17 patients studied, 2 were lost to follow up and 13 of 15 subjects improved. The tremor amplitude was reduced while the tremor frequency was not altered. Twelve

of the subjects were not receiving any other medical therapy. Three were taking propranolol and two were taking primidone 1 month before the study. It is not known if any of the patients were nonresponders to these drugs. Of note, head and leg tremor were also attenuated in addition to hand tremor reduction. Flunarizine, however, has also been reported to induce parkinsonism and hence may cause tremors.

Essential tremor is usually postural and is accentuated by voluntary movement.

Other drugs reported to be helpful in small open label series include isoniazid, clozapine, beta blockers other than propranolol, and acetazolamide.

Surgical Treatment

Sterotaxic thalamotomy with lesions placed in the Vim nucleus is effective in the treatment of severe essential tremor. This procedure is also effective in the treatment of the tremors of Parkinson's disease and tremors of cerebellar origin. The operation should be considered in patients with severe tremor that is resistant to maximal medical treatment. Unilateral thalamotomy has low morbidity and mortality. The mortality rate is less than 0.3%.¹⁹ Transient cognitive and motor deficits including hemiparesis may occur. Bilateral operations are rarely recommended since there may be permanent cognitive changes and dysarthria in up to 20% in older series. Thalamotomy is clearly the most effective treatment of arm and hand tremor, but its effect on head and vocal tremor has not been reported. Presumably the results were disappointing.

Botox

There have been recent reports on the experimental use of chemical denervation techniques in the treatment of tremors. Significant improvement in tremor has been reported in an open trial of botulinum toxin in the treatment of 51 patients with disabling tremors who had failed all previous medical or surgical interventions.²⁰ Twelve of these patients had essential tremor, 14 had dystonic tremors, 22 had a combination of dystonic and essential tremor, and one had Parkinsonian tremor. All patients had

failed optimal medical therapy and three had failed thalamotomy. All patients had tremor severe enough to cause occupational disability, impairment in activities of daily living, or unacceptable social embarrassment. There was no significant difference in peak response between the various types of tremors or between head or hand tremors. The average duration of the maximal response was 12.5 weeks. The investigators suggest that botox injection be considered in patients who have failed other forms of therapy. Such a trial is currently underway at the Brown University Parkinson's Disease and Movement Disorders Unit.

For a more detailed discussion of tremors of all etiologies, I suggest the excellent book *Tremor*, edited by Roger J. Elbe and William C. Koller, published in 1990 by Johns Hopkins University Press.

Patients and families may find useful information in the quarterly newsletter distributed by the International Tremor Foundation, 360 West Superior, Chicago, IL 60610.

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Tic Disorders of Childhood

Karen L. Kerman, MD
Louise S. Kiessling, MD

Nearly 25% of all children experience a simple or complex motor or vocal tic during their lifetime, with a mean age of onset of 7.

Tics are the most common movement disorder of children. They are involuntary motor or vocal movements that are sudden, abrupt, and often unexpected. The tics may be single or sequential movements, or sounds or phrases that may wax and wane, causing varying degrees of impairment.

Tic disorders may be classified as simple or complex; motor or vocal; and Tourette syndrome (TS). Simple tics are considered transient or acute, lasting less than 1 year, or chronic, if persisting. Habit tics, or transient tics, are simple or complex movements that generally take the form of an eye blink or a facial grimace, less frequently an isolated vocal tic such as a grunt, a throat clear, or a sniff. Often they endure for at least 2 weeks but may resolve within a year's time.

Rarely, complex tics evolve. These are movements that are performed randomly, simultaneously, or sequentially. Motor manifestations of complex tics take the form of a squat, a jump, or kicking movement, or may be vocal, consisting of repetitive, complex and stereotyped sounds or phrases. These, too, usually resolve within a year. Complex tics are 3 times more frequent in males than females. Nearly a quarter of all children experiences a simple or complex motor or vocal tic during their lifetimes, with a mean age of onset of 7.¹ Motor or vocal tics that fail to resolve over time become labeled as chronic tics.

Chronic tics may be either motor or vocal. When vocal and motor tics are seen in combination and are chronic in nature, they become classified as Tourette syndrome. TS is viewed as the most severe of complex tic disorders and the most common of the pathologic tics. The disorder is characterized by multiple motor tics and one or more vocal tics at

some point during the illness. By definition, the symptoms persist for more than 1 year. Typically, the initial manifestation of the disease is a simple tic involving the eye, face, or neck.

Characteristically, motor tics are often multiple and can involve the torso and extremities as well. Involuntary vocalizations must occur and include simple utterances of grunts, groans, or other repetitive involuntary vocalizations such as a sniff or clearing of the throat but may evolve to include more complex utterances. Coprolalia, the expression of obscene language, echolalia, repetition of what has been said, and palilalia, the repetition of a self-generated phrase or word, are examples of complex vocal tics. These complex vocalizations, however, are not necessary as diagnostic criteria for TS. Only 20% of patients with TS symptoms have a vocal tic as their initial manifestation of the disease. Coprolalia or copropraxia, obscene motor gestures, are not essential to the diagnosis of the disease and are seen in only a third of affected individuals.

It is hypothesized that infection with Group A hemolytic streptococci, and possibly other organisms, in a susceptible host may trigger a tic disorder.

Appropriate diagnosis of TS is often delayed for years with behaviors attributed to neuropsychiatric problems or allergic symptoms. Diagnosis may be further complicated by a fluctuating course with changes in the number, frequency, and complexity of tics over time. The long-term course reveals that one-third of patients have complete remittance of symptoms by adulthood; one-third have marked reduction in tics; and one-third remain unchanged or worsened. There is no known relationship to prenatal events or epilepsy. TS is believed to be inherited, possibly in an autosomal dominant mode.^{1,3} Recent work, however, suggests that an environmental trigger may play a part in some cases.² Furthermore, the presence of comorbidity with obsessive compulsive disease is well-recognized pattern in many affected families.^{1,3}

Comorbid Conditions

Since the earliest descriptions of TS by Itard in 1825, the presence of comorbid conditions has been well recognized.⁴ He described a woman who suffered from TS with complex motor and vocal tics, obsessive compulsive disorder (OCD), and severe anxiety. She was studied by other physicians over the years and was highlighted as the first of a small series of patients published in the original Tourette monograph on the disease.

OCD is a well-recognized condition in about half of TS patients. Commonly, manifestations of this disorder include compulsive touching, hand washing, checking behaviors, excessive hoarding, or magical thinking, and obsessive fears that the patient recognizes as irrational. These symptoms, like those of the TS, tend to wax and wane. These behaviors or thoughts intrude upon the individual and are viewed as senseless. The incidence of OCD in first degree relatives of TS patients is much higher than in the general population.³

A second, well-recognized comorbid disorder is Attention Deficit Hyperactivity Disorder (ADHD). It is estimated that 50% to 80% of TS patients have demonstrated ADHD in combination with the Tourette symptoms. Components of ADHD include restlessness, poor impulse control, inability to sustain attention and concentration, as well as hyperactivity. For many patients with TS, ADHD is the more disabling condition, leading to school failure and low self-esteem. Twin studies of Tourette patients reveal that ADHD symptoms often precede the appearance of tics. As a result, many of these children are treated with stimulant medication before their tics are recognized. For some of these patients, exacerbation or evolution of motor manifestation of the TS will become apparent

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ABBREVIATIONS USED

ADHD: Attention deficit hyperactivity disorder

MHRI: Memorial Hospital of Rhode Island

OCD: Obsessive compulsive disorder

TS: Tourette syndrome

in the setting of central nervous system stimulant treatment. Although there appears to be no evidence that stimulants directly cause either motor or vocal tics, 20% to 50% of patients treated with stimulants find their tics worsening.¹ For some patients, exacerbation appears to be a dose-related phenomenon with worsening of motor and vocal tics at moderate dosages. Recent work at the National Institutes of Mental Health, Child Psychiatry Branch, suggests possible reduction of tics with higher-dose stimulant use (personal communication, 1993). Most child neurologists and developmental pediatricians, however, advise conservative use of stimulant drugs in children with pre-existing tics or a family history of tics or TS. Occasionally, TS patients show symptoms of severe ADHD, requiring a combination use of central nervous system stimulants as well as medication for the tic disorder. For these patients, careful history must be obtained of pre-existing tics and family history of TS before initiation of stimulant drugs. Children on combined therapy should be monitored closely for exacerbation of their tics. Twenty percent of children with tics will demonstrate adverse effects with stimulant medication, usually within a 2 to 3-month period. If stimulant medication is required, low-dose therapy is preferred. Emergence of new tics or worsening of previously existing ones may warrant discontinuation of the medication. Alternatives to stimulant medication may be selected for this group of individuals, such as desipramine, clonidine, or a combination of the two.⁵

Appropriate diagnosis of Tourette syndrome is often delayed for years with behaviors attributed to neuropsychiatric or allergic symptoms.

Abnormalities in sleep pattern and parasomnias have long been recognized as a comorbid condition in up to half of patients with TS. These complaints include night terrors, somnambulism, insomnia, and enuresis. Tics themselves are typically reduced in number, if not abolished, in sleep and therefore do not contribute to this problem.

Manifestation of TS and associated comorbid conditions such as OCD and ADHD leads to considerable psychological stress. Depression and suicidal ideation are among the most severe psychiatric disturbances recognized to accom-

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pany this movement disorder. Klawans et al investigated behavioral disturbance in children with TS and showed that such behavior disturbances in the TS population far exceed that of the general population. Mood changes, alteration in judgment, and impulse control may be physiologic, but psychosocial and school difficulties undoubtedly play a role. Certainly behavior disturbances in TS are most prevalent and most severe in those individuals whose motor and vocal disturbances are most disabling. Behavior disturbances often improve with control of TS but studies suggest that behavior problems remain considerable and never remit to the incidence of the normal population.

Medication

The medications that have been found to be the most effective for the tic behavior are the group of dopamine antagonists that are more selective in binding to D2 receptors. Haloperidol (Haldol) is the prototypic medication of this group. In multiple studies, patients treated with haloperidol obtained good to excellent improvement in about 80% of cases. In a comparison of placebo, haloperidol and pimozide (Orap),⁷ haloperidol was slightly more effective than pimozide, and both haloperidol and pimozide were more effective than placebo. Adverse effects occur with both drugs, which were not significantly different. Significantly, though, pimozide has been shown to cause cardiac arrhythmias. The dosage for haloperidol is usually under 5 mg a day for people with TS; for pimozide, a maximum of 10 mg is suggested. It is important to note that treatment with medications is only recommended if the symptoms significantly interfere with daily life. In some cases, the obsessive compulsive or the ADHD symptoms are

more disabling than the tic disorder. In those cases, treatment for the particular disorder is indicated.

The significant side effects of the neuroleptics are important to keep in mind when treating people with TS. Specifically, akathisia, dystonic reactions and tardive dyskinesia are most troubling in childhood. Where possible, other medications with less serious side effects are being tried. Recently, desipramine and clonidine have been used for the tic disorders and ADHD with variable results.^{5,8}

Other medications are currently being considered for tic disorders, namely the opioids. At least one study suggests that naloxone ameliorates both tics and the obsessive compulsive symptoms.⁹

Anatomy

The anatomic localization of the pathways related to tic disorders are not entirely known although the basal ganglia, limbic system, and frontal cortex have all been implicated as possible sites underlying this disorder. The basal ganglia, or deep gray structures within the brain, are thought to be the central focus in this disorder in part because of their involvement in Parkinson's disease, Huntington's disease, and because of the relationship of movement disorders to the side effects of neuroleptic drugs. The basal ganglia gain access to the descending motor pathways via relays through the thalamus and motor cortex. The cortex leads to several descending pathways that eventually engage the spinal motor apparatus. The dopaminergic nigrostriatal pathway is most implicated in tic disorders.

Twenty percent of children with tics will demonstrate adverse effects with stimulant medication, usually within a 2 to 3-month period.

The basal ganglia are widely considered important in the generation and control of internally guided and sequential movements. It is the integration of basal ganglia output with cortical output that facilitates complex motor behaviors, and it has been suggested as a key locus of motor habits.¹⁰ Damage to the basal ganglia or alteration in the effectiveness of neurotransmitters or their receptors may be responsible for the release of movements that may take on the appearance of tics, tremors, chorea, and hemiballism.

When these movements are held in check, they are essential components of normal movements. One theory is that tic disorders may be produced by alterations in sensitivity of neurotransmitter receptors within the basal ganglia related to the dopaminergic nigrostriatal pathway.¹ It is important to recognize, however, that other cortical areas such as prefrontal areas and regions concerned with affective behavior also project to the basal ganglia and receive dopamine inputs and thereby may modulate motor behaviors.

Pathophysiology

The etiologies of chronic motor tics, transient tics, and TS are all unknown. There is considerable data that suggests that chronic motor tics and TS co-exist in affected families. A recent theory by Kurlan et al¹³ incorporates transient tics into the same continuum. In those families where TS is expressed, chronic motor tics are thought to represent a milder expression of the same disease. Females in these families are more likely to exhibit obsessive compulsive symptoms. Despite extensive studies of several large pedigrees, no specific gene locus has been identified.

The dopaminergic nigrostriatal pathway is most implicated in tic disorders.

Recent work has suggested a possible environmental trigger to some cases of tics, transient and chronic, as well as TS. Work at Memorial Hospital of Rhode Island and the National Institutes of Mental Health has suggested that the Group A beta hemolytic streptococcus may provide an environmental trigger in genetically susceptible families for any one of these disorders.^{2,12} There is speculation that antibodies against central nervous system cells may play a role in a cross reactive antigenic responses, contributing to the development of tics, chorea, and combinations thereof. This is thought to be the basis of the movement disorder in Sydenham's chorea.¹³

In the late 1980s, investigators at MHRI documented that children who presented at the pediatric neurodevelopmental clinic with a tic or other movement disorder were more likely to have had evidence of prior streptococcal infection than to have been on stimulant medication, which previously had been suggested as commonly associated with

tic disorders.¹⁴ They also found in a small sample (n=20) of patients with acute illness that 65% had evidence of previous streptococcal infection as indicated by elevated titers against the streptococcus or positive throat cultures for Group A beta hemolytic streptococcus. This is a 2 to 3-fold increase over previous Rhode Island levels.¹⁵ The same research group has also shown that in 1989 and 1990, children seen in their clinic with new onset or recrudescence of movement disorders were 4 to 6 times more likely to have serological antibodies to central nervous system cells than children without such tics (n=50). The study was repeated with a second group of children (n=33) with similar results.

More recently, both authors of this report have been identifying increasing numbers of children with all types of tic disorders including TS. These children are often referred because of questions of ADHD, emotional, or behavioral disorders, and tics and comorbid conditions are identified by the examiners.

It is hypothesized that infection with Group A beta hemolytic streptococci and possibly other organisms in a susceptible host may trigger a tic disorder. The genetic component may be a necessary family history for tics, OCD, ADHD, or a family history for rheumatic fever. The genetics of rheumatic fever have not been fully elucidated, but there is work by Zabriskie et al¹⁶ at Rockefeller Uni-

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versity that suggests that a marker on non T-cells may relate to susceptibility to significant infection, namely rheumatic fever or rheumatic fever with chorea. It is too early to describe fully the exact mechanism of how an infectious process can lead to cross reactivity with central nervous system cells, resulting in a chronic relapsing disorder. There is ongoing research at Memorial Hospital of Rhode Island and Brown University developing techniques to assay for these antibodies and at the same time elucidate the mechanisms of action.

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Engineered Vaccines: From Overview To a Specific Application

Helena R. Chang, MD, PhD

Harold J. Wanebo, MD

Recombinant DNA technology revolutionized the approach to developing tumor vaccines. Different strategies of antigen presenting cells (APC) engineering have been implemented. Among them, the following preclinical studies showed promise:

1. Gene encoding lymphokines and cytokines were successfully transfected into tumor cells, which resulted in augmented tumor immunogenicity.¹⁻³
2. Tumor cells of MHC class I transfectants were shown to induce tumor specific immunity.⁴⁻⁶
3. The transfectants of antisense to inhibit genes responsible for differentiation also were shown to increase tumor immunogenicity.⁷
4. Genetic constructs of either cell-based or cell-free preparations expressing high amounts of tumor antigens have been shown repeatedly as ideal candidates for engineered vaccines in cancer treatment.⁸⁻¹²

This paper will be limited to a discussion of current development in the last category of engineered vaccines.

Overview

The development of tumor immunology has been led by two theories: 1) that

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tumors possess antigen to stimulate specific immune responses, and 2) that these responses may effectively destroy target tumor cells. The progress of tumor immunotherapy has been accelerated by the recent development of hybridoma technology and the introduction of DNA recombinant technology. The former event has opened opportunities to identify and explore many novel tumor antigens and the latter technology stimulates many innovative designs of tumor vaccine.

The most discriminating antibodies are those reacting with protein epitopes on the mucin polypeptide core.

Several aberrantly expressed proteins on various tumor cells are currently being investigated for cancer vaccines. These immunogenic proteins are CEA of colon cancer,^{10,11,14} mucin core protein of breast and pancreatic cancer,^{8,15} p97 and MAGE in melanoma.^{12,16}

CEA

CEA is a 180 kD glycoprotein expressed on most gastrointestinal carcinoma. The rationale for studying CEA as a vaccine was based on the widespread presentation of this antigen on carcinomas and its targetability as shown by immunolocalization studies.^{17,18} The drawback of CEA is that it is a weak immunogen. There is little or no evidence of CEA induced humoral or cellular immunity in normal individuals or cancer patients. To overcome this problem, the recombinant vaccinia virus expressing CEA have been tested for active

The development of tumor immunology has been led by two theories: 1) that tumors possess antigen to stimulate specific immune responses; and 2) that these responses may effectively destroy target tumor cells.

immunization. The reasoning is that vaccinia virus is a strong immunogen for stimulating both humoral and cellular immunities. Vaccinia virus recombinant containing tumor antigen along with MHC antigen¹⁹ and HIV envelope glycoprotein²⁰ are among the successful examples. Kantor et al¹⁰ showed that CEA-vaccinia constructs: 1) stimulate CEA-specific humoral and cellular immunity; 2) eliminate CEA-positive tumor cells in mice; and 3) was safe and immunologically potent in a nonhuman-primate model.¹⁴ Further clinical evaluation is essential to study vaccinia virus-CEA construct in human gastrointestinal cancer, particularly human colon cancer.

Melanoma Antigen p97

Other investigators using vaccinia virus-p97 (a melanoma-associated antigen) showed similar results.^{12,21} p97 is a cell surface glycoprotein expressed at high levels in most human melanomas but only in trace amounts in normal adult tissues. The study of vaccinia-p97 in mice and monkeys showed that the immune responses were limited to the antibody response and delayed type hypersensitivity. It rarely induced the production of cytotoxic T cell response. In patients, a collaborating study by Hellström and Goodman showed that an intradermally administered single dose of vac-

ABBREVIATIONS USED

APC: antigen presenting cells
CEA: carcinoembryonic antigen
CTL: cytotoxic T lymphocytes
DNA: Deoxyribonucleic acid
HIV: Human immunodeficiency virus
MHC: Major histocompatibility

cinia-p97 failed to produce any detectable immune responses. This failure may simply be due to the immunization schedules rather than the inadequacy of the vaccine preparation.⁹

Epithelial Mucin

Mucins are large, heavily glycosylated molecules expressed and secreted by ductal epithelial cells and tumors.²²⁻²⁴ Recent molecular cloning of mucin genes from different organ sites suggest that the protein compositions are considerably different. However, there is a great similarity of the O-linked carbohydrate chains. The latter phenomenon renders some anti-mucin antibodies non-specific to either tumors or organ sites. The most discriminating antibodies are those reacting with protein epitopes on the mucin polypeptide core. The protein specific antibodies suggest that protein epitopes are indeed exposed on the highly glycosylates mucin molecules and they are clinically important.²⁵

Human tumor-reactive cytotoxic T lymphocytes are able to distinguish the mucins produced by normal and malignant cells.

Isolation and comparison of cDNA of mucins of pancreas,²⁶ breast,²⁷⁻³⁰ and large/small intestine^{31,32} suggested the existence of three genes encoding mucin molecules. The genes encoding pancreatic cancer and breast cancer are found identical in the entire sequence. This gene is designated as MUC1. The other two genes, MUC2 and MUC3, were isolated from a small intestine cDNA library and were found to be expressed in colon cancer. A unique property of human mucins is the presence of repetitive sequences of 40 to 100 tandem repeats. The amino acid residues of each tandem repeat of MUC1 consist of PDTRPAPG-STAPPAHGGVTSA. The glycosylated form of the MUC1 gene in pancreatic cancer was recognized by DU-PAN-2.²⁴ The core protein of the MUC1 gene was recognized by another monoclonal antibody SM-3. The protein epitope recognized by SM-3 consists of the first five amino acids of the tandem repeat which is exposed only in the tumor-mucin, but not the normal mucin. The hypothesized explanation for this is that incomplete glycosylation of the tumor-mucin allows the appearance of normally non-accessible protein components.³³ The aberrant

glycosylation of tumor mucins thus stimulate tumor-specific immune responses in human. Human tumor-reactive CTL (cytotoxic T lymphocytes) are able to distinguish the mucins produced by normal and malignant cells.^{8,34} The proposed mechanisms for mucin induced CTL are that: 1) the large mucins with multiple tandem repeats are capable of cross linking the T-cell receptors of CD8+ cells in a MHC-unrestricted manner; and 2) the mucin antigens are presented by the APC in association with MHC to both CD8+ and CD4+ cells. The antibodies specific to tumor mucin were also observed in patients with breast cancer (personal communication with OJ Finn.)

Proposed Cancer Vaccination with Autologous APC Transfected with MUC-1 Gene

The incidence of pancreatic cancer in the US is about 28,000 new cases a year. The 5-year survival rate of patients with such a diagnosis is estimated at 1%. Fewer than 20% of patients have surgically resectable disease. The 5-year survival rates of patients with curative resection range between 0 and 20%, with the majority of the series reporting less than 10%. From the standpoint of immunotherapy, the latter group of patients are ideal for adjuvant treatment, because of the absence of gross disease, the predictable microscopic disease, and the extremely poor survival statistics.

... autologous pancreatic cancer cells with mucin expression would be a candidate for tumor vaccination after the tumor removal.

The recently identified MUC1 gene products in pancreatic cancer have been shown to be: 1) immunogenic in pancreatic cancer patients; 2) relatively tumor specific; and 3) common in pancreatic cancer. Thus, the mucins secreted and expressed by the pancreatic cancer cells are reasonable immunogens for cancer vaccination. This suggests that the autologous pancreatic cancer cells with mucin expression would be a candidate for tumor vaccination after the tumor removal. However, pancreatic cancers are notoriously difficult to distinguish from the surrounding fibrotic and reactive tissues. The tumor can be extremely small in relationship to the entire mass. In addition, the low viability of the tumor cells

either in the native state or as a consequence of preoperative radiation and chemotherapy may adversely effect the immunogenicity of the preparation. These obstacles essentially exclude its practical use. Others have studied allogenic cell lines. However, unless the same antigen is shared by the patient's tumor and cell lines, such vaccines are useless. In addition, the dominant immune responses to allogeneic tumor may be directed against the major histocompatibility antigen instead of tumor antigen. In this case, the antitumor activity induced by cell line preparations are expected to be low. The dissatisfactions associated with vaccines prepared from autologous and allogeneic cancer cells have led to the study of alternative approaches. Finn's group has successfully transfected patient's normal cells (eg, skin fibroblasts or B lymphocytes) with MUC1 gene. The genetically engineered mucin-antigen presenting non-malignant cells eliminate the limitation of vaccine supply and the possibility of tumor growth. Additional gene transfection such as genes encoding IL-2 or g-IFN may attract the lymphocyte traffic and increase the immunogenicity of the vaccine preparation. A clinical trial using these engineered autologous APC for active specific immunotherapy in pancreatic cancer will soon be studied in Rhode Island.

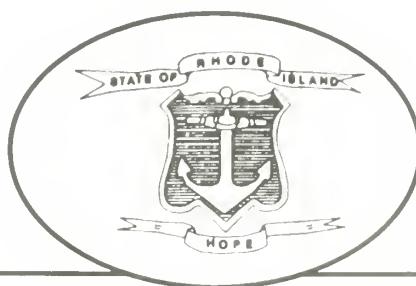
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HEALTH BY NUMBERS



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Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Prevalence of Activity Limitation in Rhode Island

The Institute of Medicine, in its 1991 report *Disability in America*, characterized disability as a costly public health problem with pervasive effects.¹ About 35 million Americans have physical or mental impairments that interfere with their daily activities; 9 million of them are unable to perform a major life activity such as working, going to school, or maintaining a household. The annual cost of disabilities nationwide exceeds \$170 billion.¹

The RI Department of Health has established the Disabilities Prevention Program under a cooperative agreement with the Centers for Disease Control and Prevention to coordinate disabilities' pre-

vention efforts in the state. The program's approach to prevention is based on a view of disability as the end result of a multi-stage process. The process begins with an *injury* or an *acute or chronic condition*, which may lead to *impairment* and, subsequently, to *functional limitation* and *disability*. Later, secondary conditions may occur as a result of the primary disability, and these may lead to further disability. One stage in this disabling process does not lead inevitably to the next, however. Appropriate care, assistive technologies, and social support are examples of factors that can slow, stop, or even reverse the disabling process.

Locally, the 1985 Rhode Island Health

Interview Survey classified 5751 respondents as either: a) unable to perform their major age-appropriate life activity; b) limited in kind or amount of major activity; c) limited in other activities; or d) not limited.² More than 15% of Rhode Islanders reported some activity limitation. The proportion reporting a major activity limitation (the first two categories) was 11.5%. In comparison, 9.4% of respondents to the 1988 National Health Interview Survey reported a major activity limitation.³

Although differences in survey methodology could contribute to the disparity, it may also be that the state has a higher rate of major activity limitation due to its

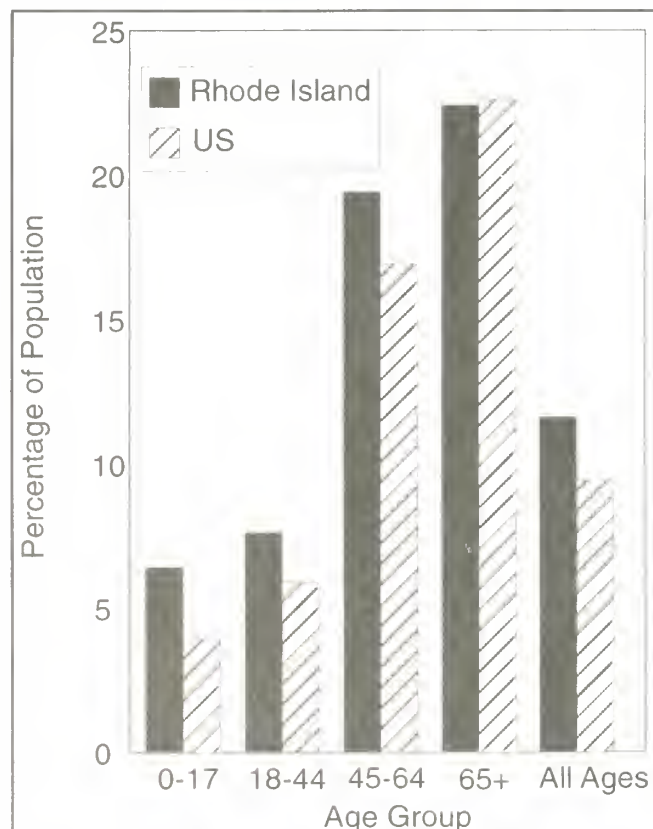


Fig 1.—Prevalence of major activity limitation RI (1985) and US (1988)

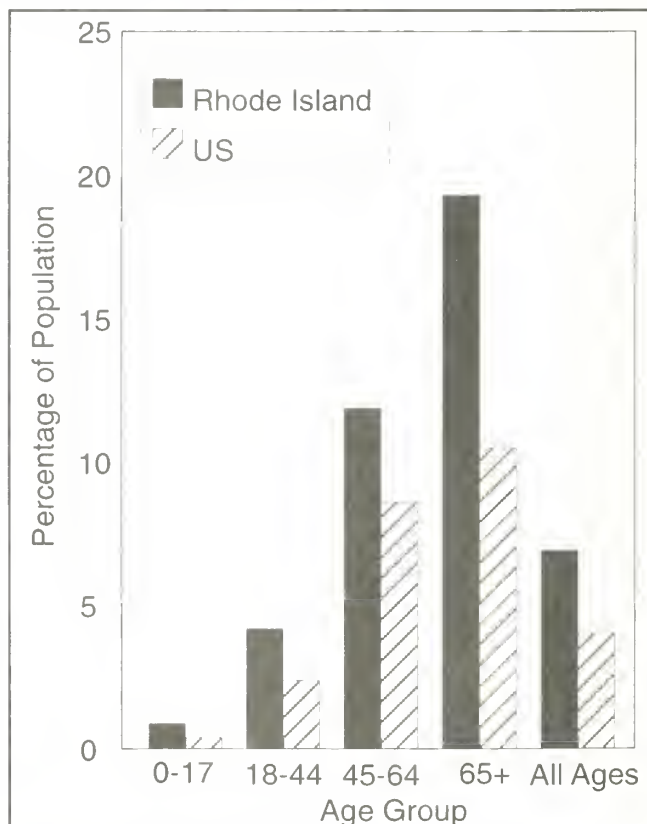


Fig 2.—Prevalence of extensive disability ("unable to perform a major activity") RI (1985) and US (1988)

Submitted by the Disabilities Prevention Program, David Hamel, MPA, project manager, Susan Feeley, MPH, epidemiologist. Health by Numbers is edited by Jay S. Buechner, PhD, and William J. Waters, Jr., PhD.

somewhat older population. Age is a major risk factor for disability, and in the Rhode Island survey the proportion of the population unable to perform a major activity rose with age (Figure 1). The state's older population does not explain the discrepancy entirely, however: in *all* age groups, the proportion with the most extensive disability ("unable to perform a major activity") was higher in Rhode Island than it was nationally (Figure 2).

Principal activities of the Disabilities Prevention Program include formation of a Disabilities Prevention Advisory Committee, support of the state's Year 2000 Health Objectives (a number of which relate to disabilities prevention), development of a statewide strategic plan for disabilities prevention, establishment of a surveillance system, and development of targeted community-based interventions.

The program's advisory committee was one of five committees that contributed to the work of the Governor's Year

2000 Health Objectives Task Force. The task force acknowledged the importance of disabilities as a public health issue by establishing the following target:

Reduce limitations as a result of chronic conditions and disabilities by:

reducing the proportion of people who experience a major activity limitation to less than 10%, and

insuring access both in delivery of services and physical environment (compliance with the Americans with Disabilities Act) for people with chronic conditions or disabilities, so that they can readily utilize prevention and intervention services.⁴

Other Year 2000 Health Objectives that contribute to the disabilities prevention effort are those concerning injuries, access to primary care, and poor birth outcomes.

In the coming months the Disabilities Prevention Program will focus on three critical activities: completion of a data book presenting hospital discharge rates for several important causes of disability,

improvement of surveillance of disabilities at the state level, and development of a statewide strategic plan for disabilities prevention. It is hoped this effort will enhance communication, coordination, and data-sharing among Rhode Islanders concerned with disabilities prevention, and ensure that the state's Year 2000 Health Objective for disabilities prevention is met.

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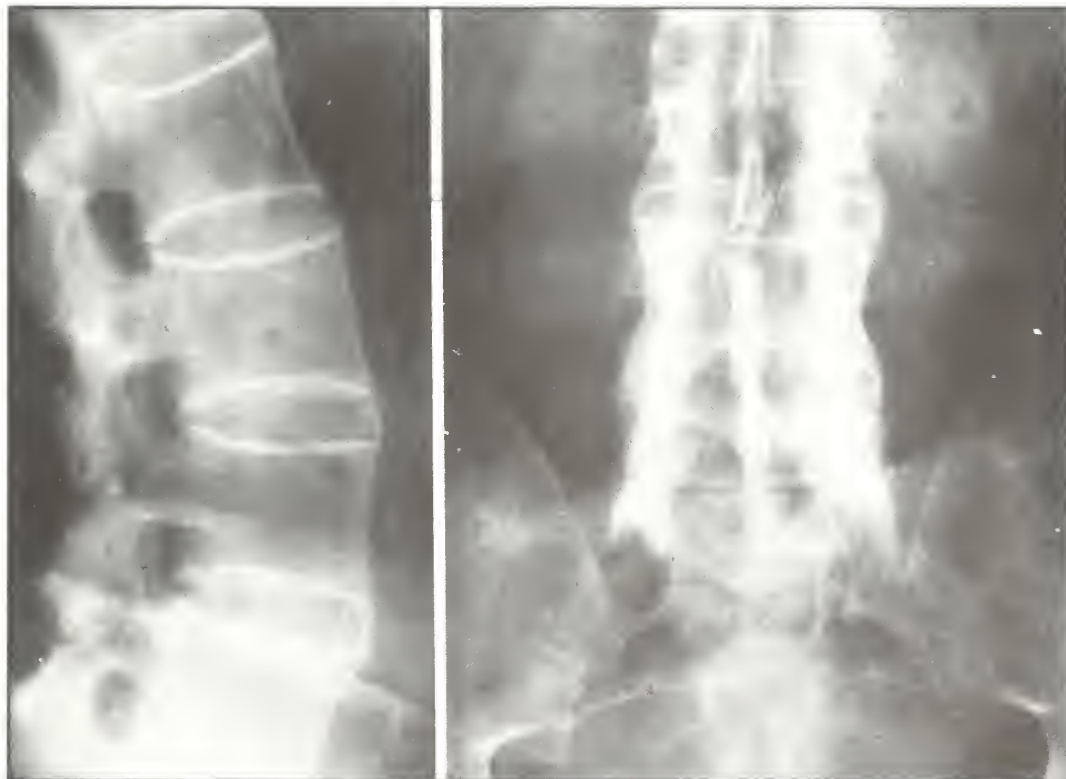
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IMAGES AND PATTERNS IN MEDICINE

Edited by
Edward R. Feller, MD

A 34-year-old man is evaluated because of a 6-month history of dull low back pain and morning stiffness improved by activity.

(For interpretation and comment, see Page 577.)



THE RHODE ISLAND MEDICAL JOURNAL

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

90 Years Ago (November 1903)

The lead article is written by Henry B. Potter, MD, and discusses tent life for consumptives in Rhode Island. The author summarizes the collective experience of many prior attempts to reverse the helplessness in the face of progressive pulmonary tuberculosis. He quotes certain classical observations such as the one by Celsus in the 3rd century: "As soon as a man shall find himself spitting and hacking on rising in the morning, he should immediately take possession of a cow, and go up into the mountains and live on the fruit of the cow." A more contemporary thought is found in Osler's statement: "Arrest or cure of tuberculosis is a question entirely of nutrition, and of the measures by which the general nutrition of the body may be encouraged the most important is fresh air." The author expresses the view that there are few dissents to this notion, but some debate nevertheless prevails regarding the best climate and the most effective altitude to accomplish arrest of the disease, consumption. Does one have to go to high altitude places such as Colorado or Saranac to achieve clinical cure? The author then describes local efforts to find a suitable place for consumption victims within the state of Rhode Island. Pine Ridge Camp, at an elevation of 600 feet was selected as a suitable place for a tent camp to house the patients. The essentials are enumerated: Fresh air; proper and abundant food given in six meals per day, with much milk; symptomatic treatments; exercise; prophylaxis such that all dejections, including sputa, are incinerated. After 13 weeks, the author presents some early but encouraging statistics showing improvement in the majority of patients; he indicates that the experiment will continue.

An article on electricity as a therapeutic agent is presented by Marcus F. Wheatland, MD. The first assumption made by the author is that electricity (whether static, galvanic, faradic or sinusoidal), like heat and light, becomes a therapeutic agent by altering the chemistry with cells. The author, while noting the value of electricity in the treatment of muscular rheumatism, concentrates his attention upon the use of this modality in gynecologic treatment particularly dysmenorrhea, amenorrhea, endometritis and pelvic inflammations. Using transpelvic electrical currents—with the indifferent electrode upon the abdomen—and 15 MA currents from a galvanic battery, most of his patients were relieved of their subjective discomforts and were returned to a healthy condition. He concludes: "In fibroid tumors of the uterus electricity will relieve the patient of all the associated symptoms, and make a decided reduction in the size of the growth, often reducing it to about one-third of its original size, but in case of large growths requiring treatments covering a long period of time, many patients tire before the end is reached and desire to be operated upon and be done with it; hence I suggest an operation in all cases unless there be some contraindications to its performance, or the patient has or is about to reach the menopause, at which time electricity seems to work more rapidly."

50 Years Ago (November 1943)

The lead article discusses the Rh Factor, its role in erythroblastosis and intra-group transfusion reactions. It is written by Edward S. Brackett, MD, and B. Earle Clarke, MD. After describing the recent (1940) discoveries by Landsteiner and Wiener of a red blood cell antigen in rhesus monkeys, the authors then pro-

vide a brief history of events leading to the recognition of the Rh blood factor system in humans and the phenomenon of isoimmunization by transfusion or through repeated pregnancies when the mother is Rh negative and the father (and fetus) are Rh positive thus leading to hemolytic crises in the fetus and the disease, erythroblastosis fetalis. They observe: "Anti Rh substances have been demonstrated in the blood of the mothers of erythroblastic infants for periods up to 3 years post partum. Cases are on record in which there was a blood transfusion reaction some years after a previous transfusion. Therefore any patient, man or woman, who has had a previous transfusion should be tested for the Rh factor and if Rh negative should be transfused with Rh negative blood and any woman who gives a history of having had an erythroblastic infant, repeated abortions, miscarriages, premature labors, stillbirths or neonatal deaths should be suspected of being Rh negative and transfused with blood from Rh negative donors. If the above precautions are observed the incidence of intra-group hemolytic transfusion reactions should be reduced by 90%. There still remain 10% that are unexplained."

The *Journal* publishes a preliminary report by the Committee on Laws of the Rhode Island Medical Society concerning a new piece of legislation amending the Social Security Act, called the Wagner-Murray-Dingle Act.

The Committee on Maternal Mortality presents an instructive case history of a woman who died minutes after the performance of a Cesarean section. Cause of death was ascribed to hyperthyroidism and mitral stenosis.

Editorials include a commentary (and statistical summary) of recent Selective Service rejections. Another editorial comments on the relatively sudden rise in the

number of births, both in Rhode Island and nationwide. Some concerns are voiced about the effects upon these growing children of an absent father — since so many are now in the armed services.

News from the war front notes that the armed services will require an additional 7000 physicians and 800 dentists “to insure even minimal care of the wounded.” With such recruitment, there should be 6.6 doctors per thousand in combat and 4.6 doctors per thousand in non-battle areas. There is news, also, about Rhode Island physicians in uniform, stationed in India, Burma, England, various Pacific islands and stateside camps.

25 Years Ago (November 1968)

The text of the first Doctor Samuel Adelson Memorial Lecture is published. It is entitled “Perspectives in Cancer Control” and is authored by Charles S. Cameron, MD, ScD. After a brief discussion of some of the newer knowledge regarding the biology of cancer, the author then asks three critical questions: “1. Is cancer control a valid objective? 2. Is early diagnosis relevant to cancer control? 3. Is early diagnosis, or better still prevention, achievable?” Before responding affirmatively to his own questions, Dr Cameron touches upon the changing, and aging, demographics of the United States and its effects upon cancer epidemiology. He then summarizes the proven

merit of exfoliative cytology for the early diagnosis of cancer and the statistical relationships between cigarette smoking and lung cancer. The utility of new procedures such as mammography and thermography are discussed. The goals of cancer prevention cannot be achieved, in his words, “While only a few are concerned, but they can be realized when enough laymen, physicians and scientists are motivated, mobilized and committed.”

Louis Leone, MD, offers a comprehensive report of 5-year survival rates for certain malignant tumors from 1956 to 1960. The neoplasms analyzed are breast, cervix, large intestine and rectum, lung, larynx, tongue and mouth. Each site is

carefully analyzed for survival per year under various interventions.

Surgical management of bony tumors of the mandible and maxilla are discussed by Leonard J. Friedman, MD.

Francis L. McNelis, MD, and Esther A. Creer, BS, discuss the highly accurate yields from cytological examination of oral secretions and bronchial washings, particularly in the identification of bronchogenic carcinoma.

Editorials include a brief commentary on recent advances in the management of hemophilia, a note on “the vanishing art of psychoanalysis,” and mention of bronilidene as a possible new antiviral agent, possibly in the treatment of influenza.

IMAGES AND PATTERNS IN MEDICINE

Interpretation and Comment
(cf Page 575)

ANKYLOSING SPONDYLITIS

This chronic, progressive arthritis is characterized by involvement of sacroiliac joints, spinal apophyseal joints, and the paravertebral soft tissues joints are affected initially by loss of definition of joint margins. The joint space progressively narrows, ending in fibrosis and bony ankylosis. The age of onset is usually late in the second decade or early in the third decade of life; approximately 90% of patients are male.

Clinically, the onset is commonly insidious with low back, sacroiliac, or hip pain. Most patients are positive for HLA-B27 antigen. Twenty to 25% of patients are affected by acute anterior uveitis. Aortic valve disease occurs in 2% to 5% of cases. Ankylosing spondylitis is 10 to 20 times more common in ulcerative colitis and Crohn's disease than in the general population. No association exists between disease activity of the arthritis and that of the associated inflammatory bowel disease.—EDWARD R. FELLER, MD

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Specifications: Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins, using 8" x 11" non-erasable bond. Tables, charts, and legends should be submitted separately from the text and referred to by number (eg, Fig. 1 or Table 2, etc.) Number pages consecutively.

To expedite production and ensure accuracy, authors are **strongly encouraged** to submit articles as well as computer-generated tables and figures on floppy diskette, formatted in any major MS-DOS or Windows wordprocessor (eg, Microsoft Word, Wordperfect, Wordstar, Xywrite, Multimate, etc.) Macintosh disks will be accepted provided text is saved in an ASCII file. If possible, Macintosh disks should be saved in DOS format, using Apple File Exchange. Diskettes must be accompanied with at least one printed copy of the manuscript. Diskettes will be returned upon request.

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3. Epstein WL. Erythema nodosum. In: Samter M, ed. *Immunological Diseases*, 2nd ed. Boston, Mass.: Little, Brown; 1971;2:944-951.

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Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin, the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle.

Antipyrine. Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol. Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect (see DOSAGE AND ADMINISTRATION: Concomitant Therapy).

Warfarin. In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time have been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine. The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin. In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin and its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil. In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear (Wallerian-like degeneration and retinal ganglion cell chromatolysis) in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagenesis tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/– mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo

The following effects have been reported with drugs in this class.

Skeletal: myopathy, rhabdomyolysis

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movements, facial palsy), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Sensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecostasia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended (see WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions).

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

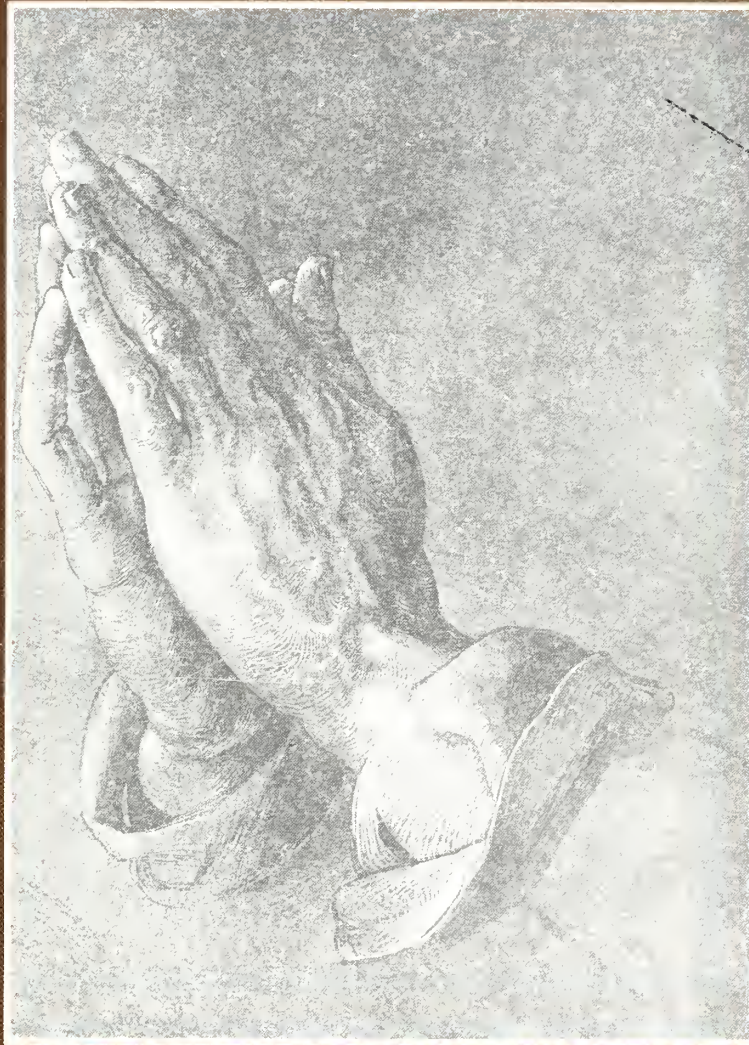


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December 1993

Volume 76, Number 12



Euthanasia



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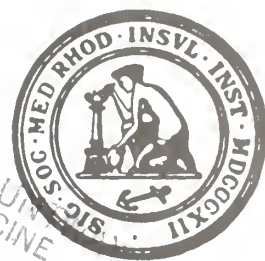
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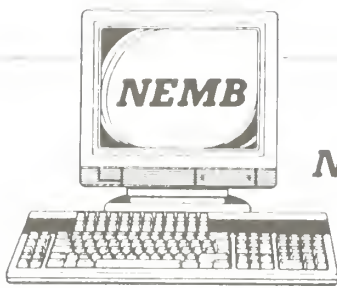
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The Shadow of Euthanasia

Children—and perhaps a few first-year medical students—believe that existence is a simple matter, understandable in terms of a few physiologic characteristics, and readily classified as belonging within one of two distinguishable boxes called either life or death. To these innocents, the role of physicians is equally clear: they are to support life relentlessly, with no consideration of the quality of the lives that they are sustaining. Death, then, becomes the sole enemy and its arrival, sure evidence of failure.

There are older physicians who will recall the practice of medicine before the development of life-extending interventions such as the intensive care unit, cardiopulmonary resuscitation and life-preserving drugs. Then, death had the controlling hand, and when it became imminent a physician's skills were reduced to an easing of the dying process and a predicting of when the end will come. It was a quiet, nonheroic encounter often with nurses, clergy and family sharing in a respectful acceptance of biological reality.

These newly devised life-extending interventions are now responsible for prolonging the *useful* existence of uncounted thousands. But they have also blurred the boundaries between life and death. In so doing, they have placed a greater moral burden upon those physicians who possess the means to alter, if only temporarily, these boundary lines.

The 1930 physician sitting helplessly at the bedside of the dying patient was but an educated observer. The 1993 physician, with access to these newer technologies, now confronts a lengthy menu of therapeutic choices; and when choices such as these can be made, then will ethical dilemmas arise.

The outsider may now accuse the modern physician of either needlessly prolonging the termination of life or, alternately, of prematurely removing life supports while

some slim hope remains. In either case, these critics will observe that the physician is "playing God," ignoring the obvious reality that virtually any medical intervention—from the prophylactic vaccination to the lifesaving surgery—will inevitably alter the natural trajectory of life. The accusation of playing God, curiously, seems to be applied only to physicians—although countless judges, military leaders, and legislators, in the sacred name of justice, national need or mere expediency, have and will undertake measures that also modify the life expectancy of countless humans.

Ignorance of the intimacies of dying and the many limitations of medicine have made the specter of euthanasia an albatross around the neck of physicians. The problem is not some sinister intent within certain physicians that must be expunged—or at the very least, guarded against. Rather, the real problem is whether society will allow the concerned physician to factor in the patient's autonomous wishes when he decides upon one course of therapy or another. In different words, shall the patient—confronting a life that has neither joy, nor meaning, nor future—have a voice in determining these therapies?

Most of this issue of the journal is devoted to a thoughtful essay on euthanasia by the eminent Rhode Island philosopher and ethicist, Professor Daniel Brock, as well as six responsive commentaries on this subject by invited members of Rhode Island's medical and religious community. The readers of *RHODE ISLAND MEDICINE* are urged to submit their views on this subject for possible publication in a future issue.

Stanley M. Aronson, MD

The Practice of the Healing Arts and the Patient

Practice, in the minds of most, is what we do to achieve eventual perfection. By tacit definition, then, those who practice are

at first imperfect but then become, through practice, the ones likeliest to reach a higher level of accomplishment. And when a young tourist, a stranger in town, asks a violin-carrying New Yorker how to get to Carnegie Hall, the answer he predictably gets is: "Practice, practice, practice."

Practice—sometimes a noun; sometimes a verb (then, more often spelled *practise*); sometimes transitive, sometimes intransitive—is a word that begs to be incorporated into pretentious adages: Practice, we are taught, makes perfect; practice, furthermore, is the best of instructors; and obviously, we are constrained to practice what we preach. The word practice, incidentally, is derived from the Greek word *praxis*, meaning action or deed, and from which such terms as apraxia are descended.

Practice seems more allied with those human attributes that are found on the positive or creative face of human behavior. Thus, we practise in the fine arts or we practise to improve athletic abilities. Also we practise (but rarely seem to reach) less tangible things such as humility, virtue, probity and healing. On the other hand, rarely do we consciously rehearse or practise evil although we do hear about such things as underhanded practices; and Scott reminds us about "the tangled web we weave when first we practise to deceive."

Practice (or its adjective, *practical*), conveys a sense of reality and immediacy. Measures become practical when they have a material, visible effect. The alternative to theory, of course, is practice; but the two rarely seem to agree: "It works in theory but not in practice." The world of gritty reality is the practical world; and the humor that is blunt, not so subtle, and at times embarrassingly direct is called a practical joke.

The word, practice, has come to mean more than the act of doing or accomplishing something. In some uses, it imparts the quality of habituation (such as the practice of smoking). When used in sports or the playing of a musical instrument, it suggests

repeated actions or exercises seeking, by repetition, to attain greater proficiency.

By the 16th century, practice was applied to the learned professions of the law and medicine ("the mysteries of mingled medicines and the practice of Physicke"). Gradually, the word came also to incorporate those upon whom the arts of healing were exerted, so that a physician, indicating the vast number of patients under his supervision, might say, "I have a large practice." Some further narrowing of this meaning of the word emerged by the 19th century when being called a practitioner suggested that the physician was a generalist rather than a specialist. In this country, a practitioner is now most commonly thought of as one who practices family medicine. Osler, who provided our profession with as many epigrams as clinical insights, tells us that one finger in the throat and one in the rectum mark the good practitioner.

Patients treated by medical students or interns will commonly take advantage of the ambiguity in meanings of the word practice and complain: "I don't want to be practised upon by young people still learning medicine." But they recover their equanimity when they learn that the physician-in-training is much more inclined to listen patiently to their extended medical histories, lengthy sagas that might well induce the recording Angel by the celestial gates to take up shorthand.

In the preceding paragraph, patient (as a noun) and patiently (as an adverb) were used to convey distinguishing meanings—yet both are derived, through the Latin *pa-*

tians, from the same Greek word meaning to suffer, to possess the capacity to endure pain without complaint. Such a stoical attitude, of course, bears little relationship to one's broader understanding of life: rarely can either the philosopher or the peasant endure a toothache with patience. When, with equanimity, we finally accept painful reality, we are then said to show patience. And for lack of any choice we somehow have elected to call this a virtue.

Patience also preserves the sense of compliance and yielding to whatever realities, often distressing, are placed upon us. The card game of solitaire is sometimes called patience because one must accept the card sequences as they are revealed (or at least accept them when being observed by another person).

Sometime during the Renaissance the levator scapulae (the muscle running between the superior cervical vertebrae and the medial margin of the scapula) became known as the muscle of patience (*patientiae musculus*) allegedly "so called from the great service of it in labour." The levator scapulae contracting coordinately with its antagonist, the trapezius, pulls the shoulders backwards. Acting in concert with other muscles attached to the scapula, the levator scapulae also causes shrugging of the shoulders. It is therefore hard to imagine which banal shoulder movement prompted some anonymous but imaginative anatomist to view it as a metaphor for patience.

But when did the human attribute called patience transform itself from adjective to noun, denoting the sufferer waiting patient-

ly in the doctor's office? One of the first uses of the word, in this sense, is found in the writings of Chaucer. In succeeding centuries a patient became more a client and progressively less a sufferer. Indeed, in today's relatively pain-free climate, about the only patience required of the patient arises during his interminable waits in a doctor's waiting room.

In this practical world where word meanings carry little permanency and less logic, patience remains critical to a practitioner's practice, particularly when with practised eye he addresses his patient's practical needs.

Stanley M. Aronson, MD

Season's Greetings

As this year of 1993 comes to a fitful close, we reserve this corner of RHODE ISLAND MEDICINE to express our hopes that the forthcoming holiday season will yield much personal joy, warmth and spiritual fulfillment for each of our readers. We hope, too, that the year ahead will be a productive and happy one.

We are sensitive to the many professional perils and mine-fields facing medicine in the year ahead, and we will make an effort to address many of these contentious challenges in the pages of this journal.

To the many faiths and beliefs represented in our professional community, the editorial board and the editors now extend their most earnest wishes for a joyous Christmas, a heartwarming Hannukah, and a merry winter solstice.

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Euthanasia

Dan W. Brock, PhD

There is an emerging consensus that competent patients, or the surrogates of incompetent patients, should be permitted to weigh the benefits and burdens of alternative life-sustaining treatments according to the patient's values, and either to refuse any treatment or to select from among available alternative treatments. More recently, significant public and professional attention has shifted from life-sustaining treatment to euthanasia and physician-assisted suicide. Unfortunately, some of the most widely publicized cases, such as those of Dr Kevorkian, have been sufficiently problematic that even most supporters of euthanasia or physician-assisted suicide did not defend the physicians' actions in them. As a result, the subsequent debate they spawned has often shed more heat than light on the subject. My aim here is to formulate and evaluate some of the central ethical arguments for and against euthanasia. Although my evaluation of the arguments leads me, with reservations, to support permitting euthanasia, my primary aim is to identify confusions in some common arguments, and problematic assumptions and claims that need more defense or data in others. My hope is to advance the debate by focusing attention on what I believe should be the real issues therein.

In the recent bioethics literature, some have endorsed physician-assisted suicide but not euthanasia.¹ Are the two sufficiently different that the moral arguments that apply to one often do not apply to the other? A paradigm case of the former is the provision by a physician of a lethal dose of medication to a patient who asks for it to end

his or her life, and who then does so. A paradigm case of euthanasia is a physician him- or herself administering the lethal dose, often when the patient is unable to do so. The only difference that need exist between the two is who actually administers the lethal dose—the physician or the patient. In each instance, the physician plays an active and necessary causal role in providing the lethal dose. In physician-assisted suicide, the patient acts “last”—for example, in the way Janet Adkins herself pushed the button after Dr Kevorkian hooked her up to his suicide machine, whereas, in euthanasia, the physician acts “last” by performing the physical equivalent of pushing the button. In both, however, the choice rests fully with the patient. In both, the patient acts “last” in the sense of retaining the right to change his or her mind until the point at which the lethal process becomes irreversible. How could there be a substantial moral difference between them, based only on this small difference in the part played by the physician in the causal process resulting in death? Of course, it might be held that the moral difference is obvious in euthanasia, the physician kills the patient, whereas, in physician-assisted suicide, the patient kills him- or herself. But this argument is misleading at best. In physician-assisted suicide, the physician and patient together kill the patient, a case of joint action for which both are responsible. I shall take the arguments evaluated below to apply both to physician-assisted suicide and to euthanasia and shall focus on euthanasia. My concern here will be with *voluntary* euthanasia only; that is, with the case in which a clearly competent patient makes a fully voluntary and persistent request for euthanasia. A last introductory point is that I will examine only secular arguments about euthanasia, though of course many people's attitudes to euthanasia are inextricable from their religious views. I take this secular focus to be appropriate for public policy.

The Central Ethical Argument for Voluntary Active Euthanasia

The central ethical argument for euthanasia is familiar: that the very same two fundamental ethical values that support the consensus on patients' rights to decide about

The central ethical argument for euthanasia is familiar: that the very same two fundamental ethical values that support the consensus on patients' rights to decide about life-sustaining treatment also support the ethical permissibility of euthanasia.

life-sustaining treatment also support the ethical permissibility of euthanasia. These values are individual self-determination or autonomy and individual well-being. By self-determination, as it bears on euthanasia, I mean people's interest in making important decisions about their lives for themselves, according to their own values or conceptions of a good life, and in being left free to act on those decisions. Respecting self-determination permits people to form and to live in accordance with their own conception of a good life and to exercise significant control over their lives. Most people are certainly much concerned about the nature of the last stage of their lives. Death is today increasingly preceded by a long period of significant physical and mental decline, due in part to the technological interventions of modern medicine. For many patients near death, maintaining the quality of one's life, avoiding great suffering, maintaining one's dignity, and ensuring that others remember us as we wish them to, become of paramount importance and outweigh merely extending one's life. Since there is no single, objectively correct answer for everyone, as to when, if at all, when one is critically or terminally ill, one's life becomes (all things considered) a burden and unwanted, the great variance among people on this question makes it especially important that individuals control the manner, circumstances, and timing of their dying and death. The other main value that supports euthanasia is individual well-being. It might seem that protecting patients' well-being conflicts with a person's self-determination when that person requests euthanasia. Life itself is commonly taken to be a central good for individuals. But when a competent patient decides to forgo all further life-sustaining treatment or requests euthanasia, life is no longer considered a benefit by that patient, but has now become a burden. Of course, sometimes there are conditions, such as clinical depression, that call into question whether the patient has made a competent choice, either to forgo life-sustaining treatment or to seek euthanasia, and a determination of incompetence

ABBREVIATION USED
ALS: *Amyotrophic lateral sclerosis*

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can warrant not honoring the patient's choice.

I emphasize that the value or right of self-determination of patients does not entitle them to compel physicians to act contrary to the physician's own moral or professional values. Physicians are moral and professional agents whose own self-determination or integrity should be respected as well. If performing euthanasia becomes legally permissible, but conflicts with a particular physician's reasonable understanding of his or her moral or professional responsibilities, the care of a patient who requests euthanasia should be transferred to another. But the ethical and policy issue is the permissibility of performing euthanasia by those who do not have moral or professional objections to it.

Opponents of euthanasia commonly offer two types of arguments against euthanasia, which they take to outweigh or to override this support of euthanasia. The first argument is that in any individual case in which a patient's self-determination and well-being do support euthanasia, it is nevertheless always ethically wrong or impermissible. The second argument grants that, in some individual cases, euthanasia may not be ethically wrong, but maintains nonetheless that ethically sound public and legal policy should never permit it. The first argument focuses on features of an individual case of euthanasia, while the second focuses on a social or legal policy that would permit euthanasia. I will initially consider the first argument.

The Argument That Euthanasia Is Always the Deliberate Killing of an Innocent Person

The claim that any individual instance of euthanasia is a case of deliberate killing of an innocent person is, with only minor qualifications, correct. Unlike forgoing life-sustaining treatment, which is commonly understood as allowing to die, euthanasia is clearly killing. Unlike providing morphine for pain relief at doses where the risk of respiratory depression and an earlier death may be a foreseen but unintended side effect of treating the patient's pain, in euthanasia the patient's death is deliberate or intended, even if in both instances the physician's ultimate end may be to respect the patient's wishes. If there is a sound ethical prohibition of all deliberate killing of an innocent person, euthanasia would be nearly always impermissible, but is such an ethical prohibition defensible?

In the context of medicine, what lends this ethical prohibition plausibility in part is the belief that nothing in the currently ac-

cepted practice of medicine is deliberate killing. Thus, according to this view, forgoing of life-sustaining treatment, whether by not starting or by stopping treatment, is allowing the patient to die, not killing, and so is not covered by the ethical prohibition against killing. Common though the view is that stopping life-sustaining treatment is allowing someone to die, I shall argue that the belief is confused and mistaken. Typical cases of stopping life-sustaining treatment are killing; they are not allowing to die, though they are cases of ethically justified killing.

Why is the common view that stopping life-sustaining treatment is allowing to die and not killing a mistaken one? Consider the case of a patient, terminally ill with amyotrophic lateral sclerosis (ALS) disease, who is completely respirator-dependent, with no hope of ever being weaned from the respirator. The patient is unquestionably competent but finds her condition intolerable and persistently requests to be removed from the respirator and allowed to die. Most people would agree that the patient's physician should respect the patient's wishes and remove her from the respirator, though this action will certainly result in the patient's death. The common understanding of what the physician does in removing the patient from the respirator is that the physician thereby allows the patient to die. But is that viewpoint correct?

Suppose the patient has a greedy and hostile son, who mistakenly believes both that his mother will never decide to stop her life-sustaining treatment and that, even if she did, her physician would not remove her from the respirator. Afraid that his inheritance will be dissipated by a long and expensive hospitalization, he enters his mother's room while she is sedated, extubates her, turns off the respirator, and she dies. Shortly thereafter, the medical staff discovers what he has done and confronts the son, who replies, "I didn't kill her; I merely allowed her to die. It was her ALS disease that caused her death." I think this answer would rightly be dismissed as transparent sophistry—the son went into his mother's room and deliberately killed her. But, of course, the son performed just the same physical actions, did just the same thing, that the physician would have done. If that is so, then the physician also kills the patient when he extubates her and stops the respirator.

I underline immediately that there are important ethical differences between what the physician and the greedy son do. First, only the physician acts with the patient's consent. Second, the physician acts with a good motive—to respect the patient's wish-

es and self-determination—whereas the son acts with a bad motive—to protect his own inheritance. Third, only the physician acts in a social role in which he is legally authorized to carry out the patient's wishes to stop treatment. These, and perhaps other, ethically important differences show that what the physician did was morally justified, whereas what the son did was morally wrong. What they do *not* show, however, is that the son killed, while the physician allowed to die. One can either kill or allow to die with or without consent, with a good or bad motive, in or not in a social role that legally authorizes one to do so.

Suppose that my argument is mistaken: that stopping life support as well as euthanasia is killing. Euthanasia, though deliberate killing, still need not, for that reason, be morally wrong. To see this point of view, we need to ask: What is it that makes paradigm cases of wrongful killing wrongful? One very plausible answer is that killing denies the victim something that he or she values greatly—continued life or a future. Moreover, since continued life is necessary for pursuing any of a person's plans and purposes, killing brings the frustration of all of these plans and desires as well. In a nutshell, wrongful killing deprives an individual of a valued future and of all that the person wanted and planned to do in that future.

A natural expression of this account of the wrongness of killing is that people have a moral right not to be killed.² But in this account of the wrongness of killing, the right not to be killed, like other rights, should be waivable when the individual makes a competent decision that continued life is no longer wanted or a good, but is instead worse than no further life at all. In this rights view of the wrongness of killing, voluntary euthanasia then does not violate that right. I turn now to the evaluation of public policy on euthanasia.

Public Policy: Would the Bad Consequences of Euthanasia Outweigh the Good?

The case against euthanasia at the policy level is stronger than that at the level of evaluation of individual cases, though even here I believe the argument is ultimately unpersuasive, or at best indecisive. There is considerable empirical or factual disagreement about what would be the consequences of a legal policy permitting euthanasia in the United States at this time, which is greatly exacerbated by the highly speculative nature of many of the feared consequences and by the general lack of firm data on the issue. There is also moral or evalua-

tive disagreement about the relative importance of different good and bad consequences. Despite these difficulties, a preliminary account of the probable main good and bad consequences should help to clarify where better data and/or more moral analysis and argument are needed, as well as where policy safeguards must be developed.

Potential Good Consequences of Permitting Euthanasia

What are the likely good consequences of making euthanasia legally permissible? First, if euthanasia were permitted, it would then be possible to respect self-determination of competent patients who want it, but now cannot get it because of its illegality. We simply do not know how many such patients and people there are. In the Netherlands, where euthanasia is legally permitted, a recent study estimated that about 2% of deaths were from euthanasia or physician-assisted suicide. No straightforward extrapolation to the United States is possible for many reasons, but, even with better data, significant moral disagreement would remain about how much weight or importance should be given to any instance of failure to respect a person's self-determination in this way.

A second good consequence of making euthanasia legally permissible benefits a much larger group. Polls of Americans have shown that a majority, of the public believes that people should have a right to obtain euthanasia if they want it.³ No doubt the vast majority of those who support this right to euthanasia will never in fact come to want it for themselves, but making euthanasia legally permissible would reassure the many who support euthanasia that, if they ever should want it, they would be able to obtain it. The legalization of euthanasia can be thought of as a kind of insurance policy that one will not be forced to endure a protracted dying process that one has come to find burdensome and unwanted, should there be no life-sustaining treatment to forgo.

A third good consequence of the legalization of euthanasia concerns patients whose lives, while they are dying, are filled with severe and unrelievable pain, and for whom euthanasia is the only release from their otherwise prolonged suffering and agony. This argument from mercy has always been the strongest argument for euthanasia in those cases to which it applies.⁴ But how often are patients forced to undergo untreatable agony which only euthanasia could relieve? It is crucial to distinguish those patients whose pain *could* be adequately relieved with modern methods of pain control, though in fact it is not, from

those whose pain is relievable only by death.⁵

Specialists in pain control—for example, in terminally ill cancer patients—argue that there are very few patients whose pain could not be adequately controlled, though sometimes at the cost of so sedating them that they are effectively unable to interact with other people or their environment. Thus, the argument from mercy in cases of physical pain can probably be met in most cases by providing adequate measures of pain relief, short of euthanasia. This goal should be a high priority, whatever our legal policy on euthanasia. Dying patients often undergo substantial psychological suffering that is not fully or even principally the result of physical pain.⁶ If the argument from mercy is extended to patients experiencing great and unrelievable psychological suffering, the numbers of patients to which it applies is much greater.

One last good consequence that proponents of legalizing euthanasia cite is that, once a decision “for death” has been made, it is often more humane to end life quickly and peacefully as can be done by euthanasia, when that end is what the patient wants. Such a death will often be seen as a better death than a more prolonged one in which the patient may be robbed of his or her dignity. Some opponents of euthanasia challenge these good consequences of permitting euthanasia, but most opponents of euthanasia cite a number of bad consequences that permitting euthanasia would or could produce.

Potential Bad Consequences of Permitting Euthanasia

I shall first consider an argument specifically against physicians performing euthanasia. The performance of euthanasia by physicians, it is said, would be incompatible with their fundamental moral and professional commitment as healers to care for patients and to protect life. If euthanasia by physicians became common, this sanction would weaken patients' trust in their physicians, as patients came to fear that a medication was intended not to treat or cure, but instead to kill. This position was forcefully stated in a paper by four prominent physicians and bioethicists:

The very soul of medicine is on trial. . . . This issue touches medicine at its moral center; if this moral center collapses, if physicians become killers or are even licensed to kill, the profession—and, therewith, each physician—will never again be worthy of trust and respect as healer and comforter and protector of life in all its frailty.

These authors go on to make clear that, while they oppose permitting anyone to perform euthanasia, their special concern is

with physicians doing so:

We call on fellow physicians to say that they will not deliberately kill. We must also say to each of our fellow physicians that we will not tolerate killing of patients and that we shall take disciplinary action against doctors who kill. And we must say to the broader community that if it insists on tolerating or legalizing active euthanasia, it will have to find nonphysicians to do its killing.⁷

How persuasive is this claim that permitting physicians to kill would undermine the very “moral center” of medicine? One point is that patients should not fear, as a consequence of *voluntary* active euthanasia becoming permissible, that their physicians will substitute a lethal injection for what patients want and believe is part of their care. If active euthanasia is truly voluntary, then no patient should fear getting it without his or her own voluntary request. Patients' fear of losing control over their care and the circumstances of their dying should be lessened, not strengthened, if euthanasia were permitted, and this policy should strengthen trust in their physicians.

Might these authors, nevertheless, be correct that, if physicians should become killers, the moral center of medicine would collapse? This question raises what, at the deepest level, should be the guiding aims of medicine, a question that obviously cannot be fully explored here. I believe that the two values of respecting patients' self-determination and promoting their well-being should guide physicians' actions as healers, comforters, and protectors of their patients' lives and should be at the “moral center” of medicine. These two values support physicians' performance of euthanasia when their patients make competent requests for it. The proper aims of medicine and the limits on physicians' power will surely be one of the central themes in the continuing debate about euthanasia.

A second possible bad consequence of permitting euthanasia is the weakening of society's commitment to provide optimal care for dying patients. We live at a time in which the control of health care costs has become, and is likely to continue to be, the dominant focus of health care policy. If euthanasia is regarded as a cheaper alternative to adequate care and treatment, then pressure may weaken to ensure that the quality of life of dying patients is appropriately maximized by providing sometimes costly support and other services. Particularly if our society comes to embrace deeper and more explicit rationing of health care, frail, elderly, and dying patients will be in a poor position to be strong and effective advocates for their own health care and other needs.

Here are two reasons for skepticism about

this argument. The first is that this same worry could have been directed at recognizing patients' or surrogates' rights to forgo life sustaining treatment. And yet, there is no persuasive evidence that the gaining by patients and surrogates of rights to forgo life-sustaining treatment caused a serious erosion in the quality of care of dying patients from either a decreased willingness of payers to fund that care or a decreased commitment of professionals or families to provide it. The second reason for skepticism about this worry is that because only a very small proportion of deaths would occur from euthanasia if it were permitted, the vast majority of critically ill and dying patients will still have to be cared for by physicians, families, and others. Permitting euthanasia should not diminish people's commitment and concern to maintain and improve the care of these patients.

The final potential bad consequence of legalizing euthanasia is the central concern of many opponents of euthanasia and, I believe, is the most serious objection to a legal policy permitting euthanasia. According to this "slippery slope" worry, although active euthanasia may be morally permissible in cases in which it is unequivocally voluntary and the patient finds his or her condition unbearable, a legal policy permitting euthanasia would inevitably lead to active euthanasia being performed in many other cases in which it would be morally wrong. In order to prevent those other wrongful cases of euthanasia, we should not permit even morally justified performance of it.

"Slippery slope" arguments of this form are problematic and difficult to evaluate.⁸ In this argument's most extreme form, permitting euthanasia is the first and fateful step down the slippery slope to Nazism, a slope that, once we are on, we will be unable to get off. Now it cannot be denied that it is *possible* that permitting euthanasia could have these fateful consequences, but that cannot be enough to warrant prohibiting an otherwise justified practice of euthanasia. A similar *possible* "slippery slope" worry could have been raised over securing competent patients' rights to decide about life support, but recent history shows such a "slippery slope" worry would have been unfounded. How *likely* and *widespread* would be the abuses and unwarranted extensions of permitting euthanasia? Opponents of euthanasia on "slippery slope" grounds have not provided the data or evidence necessary to turn their speculative concerns into well-grounded likelihoods. The character and likelihood of abuses of a legal policy permitting euthanasia depend

in significant part on the procedures put in place to protect against them, though there is not space to detail those here. It is possible to reduce substantially, though not to eliminate, the potential for abuse of a policy permitting euthanasia. Any legalization of euthanasia should only be enacted with a well considered set of procedural safeguards together with an ongoing process of evaluation of the use of euthanasia. While I believe necessary distinctions can be made, both in principle and in practice, to largely limit "slippery slope" worries, one legitimate "slippery slope" concern should be acknowledged. There is reason to expect that legalization of voluntary euthanasia might soon be followed by pressure for the legalization of some non-voluntary euthanasia of incompetent patients unable to express their own wishes. Respecting an indi-

vidual's self-determination and recognizing that continued life is not always a good for someone can support not only voluntary euthanasia, but some non-voluntary euthanasia as well. Recent history with life-sustaining treatment is instructive. There, the right of competent patients has been extended to incompetent patients and exercised by a surrogate, who is to decide as the patient would have decided in the circumstances if competent.⁹ It has been plausibly held to be unreasonable to continue life-sustaining treatment that the patient would not have wanted just because the patient now lacks the capacity to tell us so. The very same logic that has extended the right to refuse life-sustaining treatment from a competent patient to the surrogate of an incompetent patient (acting with or without a formal advance directive from the patient)

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may well do the same in the case of active euthanasia.

This potential for legalization of voluntary euthanasia, which in time could be extended to non-voluntary active euthanasia with surrogates acting for incompetent patients, is the main, legitimate "slippery slope" worry about permitting euthanasia. Even if this practice is a likely outcome, however, its ethical evaluation is more complex many opponents of euthanasia allow. Just as in the case of surrogates' decisions to forgo life-sustaining treatment for incompetent patients, so also surrogates' decisions for non-voluntary euthanasia for incompetent persons would often accurately reflect what the incompetent person would have wanted and would deny that person nothing that he or she would have considered a good. If non-voluntary active euthanasia were permitted, however, the potential for misuse and abuse would unquestionably be greater.

Concluding Comments on the Role of Physicians in Euthanasia

If euthanasia is made legally permissible, should physicians take part in it? Should only physicians be permitted to perform it, as is the case in the Netherlands? In discussing above the objection that euthanasia is incompatible with medicine's commitment to curing, caring for, and comforting patients, I argued that it is not incompatible with a proper understanding of the aims of medicine, and so need not undermine patients' trust in their physicians. If so, then physicians probably should not be prohibited, either by law or by professional norms, from taking part in legally permissible euthanasia. Most physicians in the Netherlands appear not to consider euthanasia to be incompatible with their professional commitments. There are also at least two reasons for restricting any legal permission to perform euthanasia *only* to physicians. First, physicians would inevitably be involved in some of the important procedural safeguards necessary to a defensible practice of euthanasia, such as ensuring that patients are well-informed about their condition, prognosis, and possible treatments, and ensuring that all reasonable means have been taken to improve patients' quality of life. Second, and probably more important, one necessary protection against abuse of any legalization of euthanasia is to limit who is given the authority to perform euthanasia, so that they can be held accountable for their exercise of that authority. That authority could quite reasonably be limited to physicians, whose training and profession-

al norms give some assurance that they would perform euthanasia responsibly.

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Some Reflections on Brock's "Euthanasia"

Milton W. Hamolsky, MD

The reader of my reflections upon Professor Brock's challenging essay is forewarned that: 1) I write with a 40-year background as an "academic physician"—teacher, researcher, consultant and administrator—lacking the primary, daily experiences and responsibilities of the "office-based physician" of record; and 2) major elements of my current belief system in medical ethics have evolved over the past 15 years from the ideas and teachings of Dan Brock. (I hereby absolve him for any of my errant meanderings.)

In musings about an appropriate introduction, I consulted a 1966 edition of the *Random House Dictionary* and found:

ETHICS—the body of moral principles or values governing or distinctive of a particular culture or group.

Such fundamental verity was, however, then abruptly placed in a time-perspective by the example given—"the standards of a profession: eg, It is not considered ethical for a physician to advertise." Sic transit . . .

My 1966 dictionary offered also the strictly circumscribed:

MEDICINE—the art or science of restoring or preserving health or due physical condition (no terminations here) . . . 3. the art or science of treating disease with drugs or curative substances.

My current dictionary no longer refers to advertising by physicians as unethical; the definition of medicine, however, remains the same and has not incorporated any aspect of the concept of euthanasia. My personal belief system has evolved in the opposite direction. There was no room for euthanasia (besides a sporadic case of a "mercy-killing") for me as a medical student, intern, resident, fellow, instructor, assistant professor. I shared the prevailing philosophy and behavior of doing everything you can for your patient. Today I find myself intellectually and philosophically in substantial agreement with the logic and force of Brock's major theses with, however, significant pragmatic reservations about my (or

most physicians') ability to carry out "active euthanasia" personally.

My analysis of the major factors molding such changing beliefs includes the following:

- The striking change over the past century from the paternalistic doctor-patient relationship to the sharing partnership with ultimate patient autonomy;
- The technological advances that provide to medicine the capacity to sustain biologic existence for prolonged periods and the shifting struggles of society to resolve the resultant problems;
- As a consultant, my growing comprehension of the limits, indeed the ultimate failings of our capacities to cure, our half-way therapies, our large residue of chronic diseases we can not yet understand, or reverse, or even alleviate;
- As a consultant and chief of medicine, I have shared with my colleagues the anguish of pain and suffering of our pa-

. . . permitting—and abetting—the continuation and prolongation of pain and suffering when the patient (or responsible surrogate) indicates that such a life, even with the best pain control and support systems, has lost its value and meaning, no longer fulfills my primary obligation to the patient.

tients, the torture of a certain and unrelieved future, the depression of a hopeless existence without any quality or meaning; doing "everything I can for the patient" has taken on a new meaning not limited to every technology, every laboratory testing, every pharmacologic agent;

- I have learned the reluctance of the family to initiate the approach or the verbalization of *not* "doing everything you can, doctor" and the relief, the gratitude, the willingness to confront when the caring physician first broaches the subject of other previously unspoken options;
- As the chairman of our departmental Ethics Committee I have watched families and doctors, nurses, social workers,

I have learned the reluctance of the family to initiate the approach or the verbalization of not "doing everything you can, doctor" . . .

and clergy struggle (and often succeed) in accepting the withdrawal of the respirator, the "comfort-only" consensus as the best management for a given patient, the ethically comparable, but emotionally much less acceptable termination of food and fluid;

- The slowly growing realization that "doing everything" may be the "easy way out," that permitting—and abetting—the continuation and prolongation of pain and suffering when the patient (or responsible surrogate) indicate that such a life, even with the best pain control and support systems, has lost its value and meaning no longer fulfills my primary obligation to the patient

And so I have tried to grant the fullest degrees of autonomy of choice and management in my teaching and patient care (consultative) roles, I have recommended and implemented removal of the pacemaker, comfort measures only and—later—withdrawal of fluid and food.

Thus conditioned by my experiences I am impressed by the impelling logic and intellectual force of Brock's extension of the acceptance of individual patient self-determination (autonomy) and individual well-being as the bases for his analysis of the ethics of euthanasia. Of course, if one does not accept both of these basic premises or if one's religious beliefs preclude assisted suicide, euthanasia is not an option for discussion or acceptance. I find striking parallels in these issues between discussions of euthanasia and of abortion.

Brock builds upon the willingness to consider the above two basic requisites and denies any significant moral distinction between "active" euthanasia (the physician carries out the terminal action) and "passive" euthanasia (the physician provides the means for the patient to carry out the terminal action). I believe that there is a significant difference; I have shared passive euthanasia with certain patients and I know several physicians who have found that approach morally acceptable; I have not participated in active euthanasia and most physicians I know have expressed opposition. I can accept intellectually that in either action the physician is a necessary, sharing partner, yet I cannot accept emotionally—at the present time—that the two

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actions are so comparable morally that any substantive distinction is unwarranted.

For me, the difficult element of implementation remains.

Such arguments recall again comparable issues surrounding abortion. My experiences as physician-in-chief at the Rhode Island Hospital suggest an approach to the major argument against euthanasia discussed by Brock—"the slippery slope" argument. At our hospital, before the Roe vs Wade decision, we established the policy that two or three chief or senior physicians of different services, other than the one to which the patient was admitted, would evaluate the patient (being considered for an abortion) independently and offer a recommendation for or against the procedure. In my experience, this procedure worked extremely well in effecting a consensus for the patient and her responsible physician. I believe such a model could minimize the evolution of the "slippery slope" phenomenon and add strength to Brock's carefully balanced, summarized pro-euthanasia judgment.

Brock merits medicine's respect and gratitude for his previous fundamental contributions to our thinking and resultant behavior in grappling with the complex ethical

issues of our profession and now for his courage and vision and brilliant success in his expressed aim "to formulate and evaluate some of the central ethical arguments for and against euthanasia . . . to identify confusions in some common arguments and problematic assumptions and claims that need more defense or data in others" In my judgment, he has succeeded and we are intellectually richer and individually and collectively challenged to evolve our professional ethic to grapple with what I believe will

become an increasingly important problem for medicine and society, including our patients.

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Mistaking the Periphery for the Center:

A Response to *Euthanasia* by Dan W. Brock

Janet Cooper Nelson, MEd, MDiv

One sober definition of what it is to be human is to be dying. Mortality is our common lot. No one escapes death and sacred perspective alone permits any glimpse or access to the infinite.

Dan Brock's discussion makes a significant contribution to the clarity of discourse about euthanasia. However, no new light will be shed on this dilemma until we shift the spotlight from the medical community's conduct to the patterns of conduct within American society that demonstrate our exercise of and respect for the moral agency of individuals and their communities.

Discerning normative American attitudes towards euthanasia requires a thorough discussion of the role of physicians. But this statement is not reflexive. However difficult it may be to determine appropriate professional conduct for physicians responding to their dying patients' requests, this determination does not encompass the whole of the discussion. The confusion of the two may be somewhat responsible for obscuring it.

Why do we know Kevorkian's name but not his clients'? Why has there been close analysis of the Hippocratic Oath, malpractice codes, and state statutes but not of the Mosaic Law, the Nicene Creed, or the teachings of the Qu'ran or even the dual concerns of the Constitution to prevent the establishment of religion while providing accommodation for a diversity of religious expression? What is it that rivets our attention on the ethical conduct of physicians when the moral agency, theological understandings and life circumstance of their clients are neither a matter of record nor considered primary in the legal and ethical constraints used to determine the "rightness" of death?

Physician-centered approaches to the question of euthanasia are flawed because they presume methodologically that the establishment and maintenance of standards of professional conduct for doctors will provide society the best means for preventing human harm or, stated positively, furthering human good. This notion of accountability designates the physician as the expert, and, as such, the active and responsible party, thereby nearly obliterating the choice and responsibility of the patient. It

also presumes a broader role for physicians than they actually play. Many who die, even in the clutches of menacing disease, are never seen by physicians or are only monitored medically in final moments. This distance between the dying and doctors is created by many factors including religious belief, individual choice, finance, availability of medical care, previous experience with medical treatment, ethnicity or culture, education, and class. An examination of euthanasia that presumes broad authorization or engagement of physicians with their clients is unsubstantiated and distracts from the essential ethical concerns.

The medical community routinely underestimates the extent to which their jargon, procedure, schedule, finance, and protocol are completely inaccessible to outsiders. Much of what passes for conversation, to say nothing of consent or authorization by patients of their physicians, is rooted in deference, intimidation, a hope that obedience will correlate positively with cure, and mere compliance. Is such a climate likely to foster honest discussion or debate? The widow of a world-renowned biochemist once remarked to me that her husband had never liked physicians because he was sure they knew more than he did. Can mere mortals join the discourse of such "titans"? Can such "titans" truly know the will of those to whom their art is directed?

The current societal discussion of euthanasia and assisted-suicide is simultaneously eccentric and circular, qualities that derive from the employment of categories as blurry as *physician* and *the dying* and exacerbated by the misconstrual of the physician's dilemma as synonymous with society's. Definition of categories such as *the dying* and *physician* is not easily accomplished. *The dying* cannot be identified as those for whom the threat of death is so obvious that they participate uniformly in systems of care to thwart their illness. Neither can *the dying* be defined as those for whom the urgency of their situation insures that their choices of *physician* or setting are honored or even known. The definitional implication that *the dying* and their physi-

cians have had sufficient conversation for either to know the convictions and constraints that govern the choices of the other is not even common. In fields of medicine such as oncology the discussion and process of assisting clients in their death is more common but by no means uniform. When *the dying* do turn to *physicians* for care they are treated by a population with widely varied convictions, intelligence, diagnostic ability, board certifications, experience, education, business acumen, and access to resources, making the designation *physician* far from standard.

A description of an ethics committee meeting at Hermann Hospital in Houston as reported in Lisa Belkin's book *First Do No Harm* comes to mind. The committee had gathered to hear the feelings of a young couple in preparation for a recommendation as to whether to perform surgery on their infant whose spina bifida and attendant difficulties were the worst in the hospital's history.

[The chair of the Ethics Committee] began to interrupt with a question but caught herself each time. As [the father's] words flowed, they were mesmerizing and the roomful of sophisticated, hardened professionals simply sat and stared. . . . [A pediatrician] listened and thought of [another difficult case] and of his own doubts about whether he had made the better choice. Was he doing this for himself or for [the child]? Was the committee thinking of these parents? Were they able to communicate with these parents? Or were they hearing this case because it raised sticky legal questions in the guise of medical ethics?"¹

At first hearing, this scenario may seem distant from the central concerns of euthanasia. But the similarity of the questions of the medical community and of those who watch at the bedside of dying is graphically, even poignantly, visible. Each needs to be certain that the choices they make relieve suffering, balance hope and reality well, do no harm, and do nothing to impede death's peace if no other relief can be found. Those closest to the dying act in their stead, express requests that can no longer be voiced directly, or call attention to living wills, and

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if unwritten, convey these beliefs to assist the medical staff. The question of euthanasia is rarely a single decision, nor is it, in its outworking, the solitary voice of an individual but a collaborative process. In these moments the choices that distinguish life from death are not binary and the medical community has many "colleagues" including the patient whose expertise is personal not scientific.

Dan Brock's observation may be correct that physicians cannot play the dual role of one who resists death and then one who assists inevitable death, although that conflict troubles physicians more than it bothers their patients. Within medical circles debate will continue about what role physicians can play. Some medical knowledge seems essential to qualify someone to assist suicide or perform euthanasia. However, if physicians cannot play this role, a harbinger of the professional group that could function in such a capacity is seen in the hospice movement. (It is important to note that many physicians are convinced that their codes of conduct neither explicitly provide for nor absolutely prohibit assisted suicide or euthanasia.)

The hope to keep doctor's roles and actions clear of any taint of death seems oddly inhuman. One sober definition of what it is to be human is to be dying. Mortality is our common lot. No one escapes death and sacred perspective alone permits any glimpse or access to the infinite. If the physician's art is to be truly humane, even compassionate, can it derive its stance from defiance alone? Are not physicians by definition the dying caring for the dying? Social policy development with regard to euthanasia needs an anchor in deeper more inclusive water, beyond the narrow straits governing the ethical conduct of physicians and clear of the riptides of societal scapegoating and professional narcissism.

An authentically American foundation for understanding euthanasia and assisted-suicide could be derived from a survey of the Constitution's concern to strengthen moral agency and protect individual liberty. Locating the center of this consideration in the choices of the person whose life is at stake (including the possibility of their choice of their own death) may provide a double benefit. The physician's role will be clarified without becoming dominant. Failure to establish such grounding leaves open two grave possibilities: first, that the dying person becomes a category rather than being treated as an individual at risk; and second, that the interests of the person most likely to survive the encounter (and therefore its potential legal encumbrances) will

be given priority over the concerns of the more vulnerable person. The first concern is crucial because medicine is constantly scrutinized for evidence of both its humanity and its fairness, a very delicate balance. The second concern is exacerbated by the power differential that already exists between many physicians and their patients occasioned by education, wealth, race, and gender.

Glimpsed through the lens of the US Constitution, the debate over euthanasia is best focused by two concerns: the sanctity of personal liberty, and the requirement that the state neither establish any religious mode nor fail to accommodate a diversity of religious expression. The issue of personal liberty has always been balanced against the interests of the state to preserve the peace and safety of the community, hence

gun laws, zoning, and environmental legislation. Religious questions have been more complicated. The decision to prohibit legally Native American religious practice, including healing rituals for more than 150 years of the nation's history speaks more to governing by prejudice than the Constitution. These matters only become more passionate and less legally clear when the conduct of a young Christian Science couple who practiced their religious tradition's healing is seen to have resulted in the death of their tiny son. Where does the need to insure religious liberty collide with the interests of the state to protect life? Which principle takes precedence? What risks engendered by religious conviction may someone take without incurring the intrusion of the state? How devout may a believer be without the state determining that that is too

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devout? Shall we understand the Constitution to say that religious practice is protected by the state unless death is the issue? Can the right of individuals to choose their individual death be protected without setting at risk the responsibility of the state to protect life? What conditions would have to pertain? How can they be demonstrated? These and other questions must be considered carefully.

Beverly Wildung Harrison writes: "some believe that to invoke the principle of respect for human life settles the matter, stops debate, and precludes [a] single, simple act. . . . By contrast, many of us believe the breadth of the principle opens up to reconsideration the question of what the essential moral quality of human life is all about and to increase moral seriousness about choosing . . ." ² These thoughts are included within a chapter entitled "Theology and Morality of Procreative Choice," and are directed at clarifying the American discussion about abortion. She suggests a principle of "bodily integrity," ² which rejects the primacy of pregnancy, fetal life or abortion and insists that the whole of a woman's life especially the independent voice of her moral agency be included in any adequate ethical matrix. By extension from the abortion discussion Harrison's principle of bodily integrity suggests a rubric for the euthanasia debate. Neither the medical community's need to define itself apart from any agency of death nor the need for society to answer the request of the dying to die may be given primacy. "Bodily integrity" and particularly the challenge to include in the ethical matrix the voice of individual moral agency, suggests that we might productively reframe the euthanasia question to ask on what basis we would fail to honor the choice of the dying to die? Would not any ethical system that failed to respect an individual's decision to die when faced with terminal illness rightly be termed coercive?

Other designations for such an ethical system might be holy, orthodox, or true. Although I am theologically interested in these categories, as I peer out from the midst of my own bodily integrity, I observe a variety of forces in American eager to convince me that their category, their formulation is ultimate, and I worry. James Davison Hunter describes the phenomenon this way:

What is ultimately at issue, then, are not just disagreements about "values" or "opinions." Such language misconstrues the nature of moral commitment. Such language in the end reduces morality to preferences and cultural whim. What is ultimately at issue are deeply rooted and fundamentally different understandings of being and purpose. ³

The euthanasia dilemma sits amid a much larger dispute that threatens to tear apart, but may also contain the promise to reweave the fabric of American self-definition. Given the passion and depth with which individual voices speak in this discourse it seems unwise to prejudice the outcome by confusing the outsized voice and prestige of the medical community with that of American society as a whole. The medical community could assist discourse by the use of its educational, research and public health structures to encourage the participation of the public in the shaping of health care and to stress physician instruction in the art of primary care. These measures protected by our elegantly spare constitutional structures hold the greatest potential for insuring that the dying are cared for within an ethical

context that honors their choice and for honoring the visions of eternity and compassion that reside in mortal imaginations.

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Euthanasia—Why Not?

Paul Conner, OP

Western cultures must face a shifting social attitude about life and death. Not long ago, euthanasia was seen popularly as an inhumane solution to any problem whatsoever. Today, however, growing public opinion views euthanasia as the only humane solution to certain problems. In this article, we will look at the problems which underlie such a shift in attitude and also look beyond euthanasia for genuinely humane solutions to these problems. Along the way, we will reformulate the latest development in classical ethical reasoning about our obligation to preserve human life, and we will review the current debate about this obligation in regard to providing nutrition and hydration or withholding them from permanently unconscious patients.

Multiple signs indicate that if western peoples, particularly in the developed countries, are going to stand steadfastly against euthanasia, they will do so only if they also are set firmly against homicide, genocide, suicide, and indiscriminate war. This assertion is neither thoughtless, nor calculated exaggeration. It is based, first, on the dictionary meaning of these several terms which involve "killing" or "murder." Second, it is based on a startling human variety: some people today are against killing for any reason; others are for killing for various reasons; yet others are simply confused about euthanasia as such.

Everyone knows the ethical meanings of homicide, genocide, suicide, and indiscriminate war. But "euthanasia" is a somewhat foreign term made up of two Greek words meaning "good death." Today, however, the precise ethical meaning of euthanasia is: an action (such as an injection) or an omission (such as "pulling the plug or tube")

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which of itself or by intention causes the death of a person, in order to eliminate the pain and suffering he or she is experiencing.

Rightly impressed by the noble ulterior motive of removing unbearable pain and suffering, people can overlook the immediate goal of taking a life to do so. This is why euthanasia has popularly been called "mercy killing," a misleading term because the "mercy" involved, even though it may be sincere, ends up disrespecting most of human dignity. This "mercy" is only feeling-deep, on the level of pain and suffering. Perhaps it should rather be called "pity." Pity connotes more a response to bodily and emotional values than to those of personhood and of personal truth, goodness, and beauty, let alone to any values of genuine religion. For these and other more pragmatic reasons we shall discuss, today's popular euthanasia is simply medical homicide.

Partly because many Americans do not see that euthanasia is killing or murder, but partly also because others see killing as ethically acceptable in special cases, our generation in the United States is at the door step of an era in which euthanasia is being turned to across the land to "solve" pressing human problems. Events and polls show that already a majority of Americans see no other solutions.¹

The narrow failures of Initiative 119 in Washington State in 1991 and of Proposition 161 in California in 1992 reveal the spreading mentality for euthanasia. So does the call for assisted-suicide by Dr Jack Kevorkian with his "death-machines" and numerous "assists," and Dr Timothy Quill with his political lobby for medically assisted suicide, as does the popularization of suicide in Derek Humphry's best-selling *Final Exit*. Killing human beings is more and more the only answer our culture can come up with for certain human problems.

What are these problems?

Fears

The greatest general problem seems to be growing fears among people about how their lives might end.

Besides the perennial fear of death itself, a contemporary fear people have is that they will become prisoners of the awesome de-

... if western peoples, particularly in the developed countries, are going to stand steadfastly against euthanasia, they will do so only if they also are set firmly against homicide, genocide, suicide, and indiscriminate war.

velopments of medical technology. They fear losing personal control of their own dying, for example, by being left interminably "on a machine." These people—whether they are simply old and feeble, or have a terminal disease, or are the victims of tragic accidents—want to die naturally when their time comes. Moreover, they do not want to become useless or unwanted burdens or have their resources and those of their families and of society exhausted just to keep them alive in "a vegetative state."

Another spreading fear among people is that they will die in some protracted, painful, and undignified way. Understandably, our comfortable western society has developed an overpowering aversion to pain and suffering, on the one hand, and more and more people live alienated from family and friends and must face dying alone, on the other hand. For both reasons, they are afraid.

Finally, there is the strange fear among more and more people, especially many who are young, that their lives are not worth living. They feel so little self-esteem that they are afraid to live. Repeated rejection, failure, and lack of affirmation, or simply lack of goals to live for, have left them chronically despondent. Nothing convinces them that they should live despite their fears, and thus they claim a so-called "right to die" when and how they wish.

Costs

A second general problem for which euthanasia seems the only solution to many today is the spiraling costs of keeping weak, seriously disadvantaged, and very sick people of any age alive. It is often noted that in the United States the elderly, who are living longer and longer, use three and one half times the medical resources employed by everyone younger and consume fully half of the available pharmaceuticals. The average cost of intensive care for each premature infant is \$25,000.² The average expense for the first year of care for each PVS case, or patient in a "persistent vegetative state," is about \$250,000.³

Disadvantaged Children

A third problem for which euthanasia seems the only solution for many parents

and health care providers is the increasingly early discovery of defects in pre-born and just-born infants, defects either already present or genetically programmed to develop. This knowledge, which ultimately parents must face, and medicine's increasing ability to keep severely disadvantaged children alive for years, have occasioned many abortions and infanticides in this country and continue to do so. These killings done to eliminate suffering of the children are euthanasia in a full sense, while those done to eliminate suffering more for parents than for the children killed, and to eliminate expense for society, are euthanasia in an extended sense.

Ethics and Christ's Guidance

The above are severe human problems. Only love-motivated and truth-filled thinking will solve them in humane, Christian ways. Killing is a short-sighted, false solution to these problems because ethical solutions adequate to human reason and to the facts exist for every human problem. Our western heritage has refined a consistent ethic which helps evaluate competently even the complexity of contemporary medical choices and, at the same time, carry forward the refining of that ethical vision and its principles. The heritage of specifically Catholic ethics stimulates and enriches this process of applying unchanging principles of human reality to ever-changing human situations.

In mid-March 1992, for example, at an International Congress in Rome on death and dying, John Paul II pinpointed two extremes that clear ethical thinking must circumvent. He said simply, "We must avoid both euthanasia and over-treatment."⁴ The Holy Father is telling the world not to kill but also to let people die when they should. In trying to put together truth-filled solutions which avoid these extremes of euthanasia and over-treatment for each of the above problems, appropriate ethical principles and insights from our western heritage will emerge.

Fear of Being in a "Vegetative State"

An ethical solution to the fear of becoming a helpless prisoner of medical technology is the focus of a federal law which took effect December 1, 1991.⁵ The law provides that every patient who enters a health care facility funded at least in part by taxes must be informed about and helped to determine what are called "advance directives," namely, decisions about what medical care is or is not to be used if and when the patient becomes and remains unconscious.

An older directive known popularly as the "living will" has caused untold confusion and misinterpretation. In the form of a checklist of what specific treatments the patient wanted and did not want, this primitive directive pretended to foresee the potentially highly variable circumstances of the patient's changing condition, and the advisability of treatment choices.⁶

The new advance directives urge patients, instead, to discuss their mind and wishes with a trusted family member or friend who they designate as their "proxy" health care decider, or what is known legally as agent with "durable power of attorney."⁷ This proxy would then apply the patient's mind and wishes to the ever-changing health situation and make decisions, in pursuit of the patient's best interests, for or against medically proposed means of treatment.

Another spreading fear among people is that will die in some protracted, painful and undignified way.

Under the new law, however, advance directives remain a patient's option. Yet, done in the right way—with an ethically informed conscience—they are strongly recommended as one responsible step in caring for one's life. Practically, they are also a good way of exercising personal control over one's dying under God, even should one become unable to communicate.

Ethical or Unethical Treatment

In order for either the patient, when able, or the patient's proxy to make a wise, responsible decision for or against proposed means of treatment, both theoretical principles and practical insights of medical ethics—long tested by western civilization—are needed so that solely fears or other emotions, ignorance, pressures from others, or monetary concerns do not make these decisions.

The *principles* needed are unchanging truths about our humanness. These provide needed objectivity for the decision. One such pivotal principle is that of *human stewardship* (not ownership) *of our very lives*. This principle precludes doing whatever we might wish with human life, our own and that of others, and insists, rather, on our fundamental, personal responsibility to care for all human life intelligently and creatively, bound only by respect for its nature and purpose and by our limitations. A primary consequence of this principle is that every person is obliged ethically to take care of his or her life and health in ordinarily possible,

beneficial ways, but not in ways ordinarily impossible or seriously burdensome.

The practical *insight* needed as guide is a prudential application of the above principle, its ethical consequence, and other related principles to each concrete case. Genuine prudence provides the flexibility demanded by circumstances, which are variable case by case. This prudential insight decides whether, in the present circumstances, the treatment which the physician proposes is an *ethically* "ordinary" way or means (that is, one possible and "proportionately" beneficial in view of the burdens expected) or an *ethically* "extraordinary" way (that is, one "disproportionately" burdensome) for the patient or proxy to care for the patient's life.

In order that ethical principles and insight guide decisions correctly, *all* relevant circumstances must be weighed, not just the medical diagnosis, treatment, and prognosis, although these are primary considerations. Relevant circumstances could be: the patient's need and will to live; religious values; the patient's and family's abilities to endure the treatment; the patient's, family's, or society's means to pay costs; and so on.

Each circumstance is assessed on its own merits as beneficial and burdensome. Then, all these circumstances are weighed together for an overall prudential, ethical judgment that this medically proposed means of treatment is either more beneficial or burdensome—all things having been considered.⁸

To clarify how this *ethical* judgment is so much more complete than just the physician's *medical* judgment, it can be expressed as a *formula of considering several variable elements*. At least 11 of these elements are proposed as common circumstances by the Vatican's *Decree on Euthanasia*, although, as that document notes, special cases may involve yet other circumstances. An outline of these common elements (numbered consecutively along the left margin and italicized in the outline) and of the formula of considerations for making a prudential health care decision could be constructed in the following way.

I. TREATMENT VARIABLES

#1: A. The initial consideration should be about the "type" of treatment proposed, that is, the *ethical nature itself of the treatment* (for example, abortion and euthanasia are unethical types; resuscitation and surgical restoration of function are ethical, or at least ethically neutral, types of treatment). This *first* element is the "moral object" of the patient's health care decision, that is, the objective

ethical purpose of the specific medical means.

- B. Around this type of treatment may be clustered one or more of the following medical and possibly ethical circumstances (elements #2-#12).

The first five of these circumstances (elements #2-#6) are treatment variables, and, taken physically, they together with the treatment make up the *medical meaning* of "ordinary means" (that is, "standard medical practice" in a given setting) or "extraordinary means" (non-standard practice).

- #2: 1. *Benefits forecast*: such as curing, restoring consciousness or function, maintaining life with the hope of recovery, slowing or remission of disease, or reducing undesired pain.
 #3: 2. *Risk* to the patient from the treatment (some burden of loss: such as appearance, function, or life).
 #4: 3. *Possibility* of using the proposed treatment (such as availability of qualified personnel, equipment, transplant tissue or organs, and so forth).
 #5: 4. Degree of complexity of the treatment (for example, several stages over a long time).
 #6: 5. Financial cost to the patient, family, and society.

II. STATE-OF-THE-PATIENT VARIABLES (POSSIBLE BURDENS)

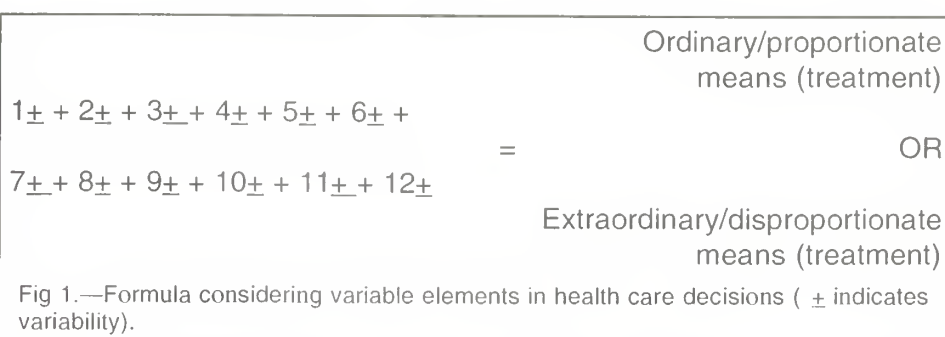
Can the patient bear the pain and suffering of the treatment in view of his or her:

- #7: A. *Physical and psychological resources*?
 #8: B. *Moral resources*?
 #9: C. *Personal desires* (the ethical circumstance of *motive*): such as to assume the responsibility of using ethically ordinary means or of foregoing extraordinary means in order to accept "the human condition," or to avoid means whose burden he or she judges disproportionate to beneficial results, or not to impose excessive expense on the family or on the community?

III. OTHER VARIABLES (BURDENS FOR OTHERS)

- #10: A. *For family* (for example, stress, cost).
 #11: B. *For health care staff* (for example, stress, insufficient personnel).
 #12: C. *For society* (for example, cost or restriction on space, service, equipment, or medication).

The formula itself of considering these common variable elements in order to make a prudential health care decision, which the above outline details, could be represented in a mathematical way (Figure 1).



If judged more beneficial than burdensome, by use of the above formula for considering all relevant elements, the proposed treatment is ordinarily possible or "proportionate" and thus ethically obligatory; the patient or proxy should choose it. If judged more burdensome than beneficial, however, the treatment is ethically extraordinary or disproportionate and is non-obligatory.

Extraordinary or disproportionate treatment may be chosen, nevertheless, if good reasons justify bearing the expected burdens. Examples of such reasons would be keeping a dying person alive long enough to fulfill obligations to God, to family, and to others or to try some experimental treatment which has been knowingly consented to and which may benefit the patient or, at least, humankind.

The above theoretical principles and prudential insight guide decisions about *all medical treatment of all patients in all circumstances*, not just those in circumstances more likely to invite the false solution of euthanasia.

Therefore, if costs are truly prohibitive for patient, family, or society, as an example, the treatment is ethically non-obligatory. Barring other justifying reasons, the patient *should* be allowed to die with love and comfort *but without* this medical means.

Similarly, if the treatment is severely repulsive to the patient, it may ethically be refused or withdrawn, even if death is foreseen, though not wanted, and occurs.

And, of course, if the proposed treatment would not counteract a disease but only delay approaching death, it is medically ineffective and ethically "futile." The Vatican *Declaration on Euthanasia* states that an immanently dying person may "refuse forms of treatment that would only secure a precarious and burdensome prolongation of life, so long as the normal care due to the sick person in similar cases is not interrupted."⁹ At its conclusion the *Declaration* indicates that such care includes the "comfort of boundless kindness and heartfelt charity."¹⁰ In this immediate context, useless treatment may not be chosen without a justifying reason because it would add at

least the burden of keeping the patient from concluding his or her life naturally. For a Christian, this ethically non-justifiable, extraordinary treatment would forestall his or her eternal reward. Even to keep the patient slowly dying in a vegetative state—to change the example to that of death being inevitable, owing to an incurable disease, but not immanent—*may well* be disproportionately burdensome to the dying patient and, in terms of strain and resources, to the family, medical personnel, and community.

One situation which makes most difficult the judgment about whether or not treatment or care is useless is becoming widespread. This is the situation of certain permanently unconscious patients needing medically assisted nutrition and hydration to remain alive.

Means of Care: Nutrition and Hydration—Two Opinions

The debate about whether or not to withhold or withdraw food and fluids from such patients rages currently in both secular and religious quarters.¹¹ The morality of either side of this question has not yet been fully resolved by the Catholic Church. In fact, not only are reputable Catholic theologians at variance on the matter, but groups of American bishops have issued documents with opposing conclusions. The bishops of Washington State, Oregon, and Texas think that food and water can be withdrawn ethically from many terminal, unconscious patients for the right reasons.¹² The bishops of New Jersey, Pennsylvania, and Massachusetts think that food and water may almost never be omitted.¹³ A 9,000-word statement entitled "Nutrition and Hydration: Moral and Pastoral Reflections" was released publicly on April 2, 1992, by the 21-bishop Committee for Pro-Life Activities of the National Conference of Catholic Bishops.¹⁴ It took the committee, chaired by Cardinal O'Connor, 4 years to formulate the document, yet the bishops style it as "our first word, not our last word on some of the complex questions involved in this subject."¹⁵ Their statement reviews both positions and leaves the door open for both.

Nevertheless, because of a greater persuasiveness for the committee of the argument for providing medically assisted nutrition and hydration whenever they are capable of sustaining life, and because of a growing practice across the land of euthanasia for permanently unconscious patients, the committee urges Catholics to be "guided by a presumption in favor of medically assisted nutrition and hydration."¹⁶

In this spirit, I will attempt to summarize the main points of bishops and theologians who think that food and water must nearly always be provided the dying person.

This *line of thought* is based on a very good reason. The reason is twofold: that human life is of worth superior to any other on earth, and that we are only stewards of it (not those who give or take life). The line of thought is that food and fluids, even medically supplied, are so necessary to life that they are always ethically ordinary means of caring for it (except in the rare case when food and fluids themselves cannot be assimilated by the dying patient and are a direct burden). Because of the superior value of human life, it is always a great benefit to sustain it by ordinary means. To withhold or withdraw food and fluids, however, causes death and is, therefore, killing. When this is done with the intention to kill in order to stop suffering, it is also euthanasia. Consequently, until death takes each person from our care, we must sustain even terminal patients with nutrition and hydration.

A summarized response to this opinion, which is also ethically acceptable unless the Church excludes it in the future, is not that human life at its weakest is no longer of superior value nor that we do not always have an absolute ethical obligation to take care of human life. Rather, the response highlights these points: 1) our ability to care for human life is limited to what is practically possible to us; 2) allowing a person to die from an underlying disease we can do nothing about is not taking a life or killing; 3) to withhold or withdraw nutrition and hydration in such irreversibly terminal cases is not to be the cause of death; and 4) such withholding or withdrawing of food and fluids can well be part of the loving care that we are ethically bound to give.

In these cases, in fact, to continue food and water is not to sustain life but to prolong needlessly the dying process, and one needs a justifying reason to make dying persons, their families, health care personnel, and society endure such a burden.

Remember, both lines of thought, or theological opinions, fall within acceptable Catholic teaching at this point in time, but the American bishops urge a presumption in favor of the first opinion. Notice that both

opinions are set against euthanasia. They differ only on: 1) whether to keep a dying person alive, in the circumstances described, is a benefit or a burden; and 2) whether food and fluids are always obligatory or not. Catholics are free at this time to follow whichever opinion is more persuasive to them.

Fear of Pain and Suffering

An ethical solution to the fear of a protracted, painful, undignified death is: advance directives for adequate pain management and for hospice care.

Contemporary analgesics remove (until a peaceful death) the former burden of pain in as many as 95% of all cases.¹⁷ Not all physicians are competent in this developing field of pain management, however, nor are all willing to spend the considerable time it takes to adjust care to the patient's changing condition. People aware of modern analgesic capability, nevertheless, have an enlightened answer for euthanasia as the solution to pain: "Why kill because of unbearable pain," they can say, "when we know how to manage pain pharmaceutically and humanely?"

A relatively rare case of pain relief may cause confusion about euthanasia and should be mentioned here. This case occurs when unendurable pain cannot be relieved except by administering a drug, such as morphine, in so strong a dosage that, as a side effect of removing pain, the drug shortens the life of the terminal patient. Notice that a shortening of life is not wanted or sought but is only tolerated as an unavoidable side effect of what is wanted, namely, the reduction of pain. No direct or wanted killing or euthanasia is involved; hence, such pain management would, of itself, be an ethical option.

In our day, these infrequent cases are becoming even more rare because of hospice care. People experienced in hospice care of dying patients, loving care coupled with competent pain management, know hardly any cases whatever of unbearable pain and suffering during the dying process. One major reason for this wonderful fact is that pain and suffering are lessened noticeably for patients who experience normal human interest and affection until they die, but are heightened for patients who face death alone, no matter the technological comforts administered to them.¹⁸

The "Right to Die"

So much in our present western culture betrays our fading abilities to detect and to respect the value and dignity of human life. Those who think they have a right to take dying into their own hands, for example, do

not value their very lives more than feelings resulting from suffering and their autonomy to make free decisions. They think that feelings and autonomy alone are decisive, not other values of greater import, such as responsibility for their lives to those who love them, to society, and to God.

Their example of solving problems by so-called "rational suicide" or assisted suicide, also called "aid-in-dying," increases public opinion that some lives are not worth living because they are burdens, whereas in truth, life itself, aside from what may torment it, is never a burden. Suicidal example puts pressure on the elderly and weak to end their lives similarly and on parents of disadvantaged children not to let them live. These "solutions" only deepen our culture of death.

But Christians build a culture of life. Besides believing that life and death should remain in the hands of God, the Christian knows that he or she can grow in character despite whatever challenge. In union with Jesus, pain, suffering, or dying can give great meaning and value to living. In addition to fidelity to God and to oneself, a Christian can remain faithful to family and friends, at the very least by leaving them the example of growing as a person through even the most negative of experiences.

Cost

Given the fact that in the United States we spend much more per capita than any other country on health care (13% of our GNP or about \$2 billion per day, \$23,000 per second),¹⁹ there remain two astonishing injustices. The first is that some 37 million of our population cannot afford insurance for even basic health care and another 60 to 70 million have inadequate insurance for basic care.²⁰ The second injustice is that costs for any health care are out of control.²¹

None of us singly can solve these enormous social injustices. It will take all of us as thinking, vocal, and voting citizens to pressure legislators to work out reasonable controls and distribution of resources, starting with basic health care for all citizens.

Nonetheless, each of us can and must deal with the circumstance of cost in our health care decisions. We face the same question in many other settings when we ask ourselves, "Can I afford this VCR, this vacation, this dress or suit of clothes?" We must discern decisions about care of our health just as realistically, "Can I afford, can my family afford, can my society afford this treatment?" It is a matter of common-sense budget-thinking about whether the treatment is proportionate or disproportionate to available resources. What are my real

limits? Does cost make the treatment ordinary for me and therefore ethically obligatory, or extraordinary and ethically optional, such that only good reasons would justify the over-expense?

People can cheat on one side or the other of common-sense spending. Governments and health care institutions can do the same. Yet, if fiscal responsibility were given its fair place in health care decisions in the United States alone, it has been estimated that \$200 BILLION would be saved each year, for this amount is currently wasted on unnecessary testing, procedures, and fraud.²² Fraud itself accounts for 10 cents of every health care dollar.²³ Then, there is the waste of unused facilities, reduplication of high tech equipment among competitive providers, exorbitant drug pricing,²⁴ and unreasonable malpractice risks which cause the pervasive practice of "defensive" medicine.²⁵ Moreover, a survey published in *Scientific American* reveals that the salaries of physicians in the United States are five times the average income, a proportion far higher than in every other developed country, including Australia, Canada, France, Italy, Japan, Sweden, Switzerland, the United Kingdom, and West Germany.²⁶

Disadvantaged Children

From what has been said above, it should be evident that an ethical solution to the problem of disadvantaged pre-born and new-born children would include at least the following considerations: a) always choosing care that is ordinary or proportionate in terms of benefits over burdens for the child first and foremost, but also for the family and society; b) choosing against unjustified extraordinary care (disproportionate to expected benefits); c) when the ethical judgment of proportionate or disproportionate means is doubtful, which can happen frequently in cases of newborn children, presumption for choosing the treatment should prevail; and d) placing unwanted children for adoption.

Conclusion: Ignorance and Cowardice

Another problem, so far unmentioned, underlies the trend toward euthanasia in the United States and throughout the western world. This more basic problem is ignorance of a reasonable, ethical solution to these and other problems and/or lack of courage to choose and to follow out ethically sound solutions.

Before ignorance of our western moral heritage becomes hardened prejudice, it is vital to educate minds still open to insight about human dignity and the reasonable-

ness of genuine ethical thinking.

With such thinking as guide and courage behind ethical choice, health care decisions will unswervingly respect full human dignity, always direct care for the sick in rightful view of our actual limitations, and, therefore, let people die when there is nothing we can reasonably do to help but love them.

(NOTE: For a complete list of references for this article, please contact the Managing

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The Voice of God

Rabbi James Rosenberg, MAHL

Call her Ruth. At first the doctors thought she had Parkinson's disease. A second diagnosis was far more grim; Ruth was suffering from a devastating form of progressive paralysis. Over the next year or two Ruth would become totally rigid. She would lose the ability to move or to control her bowels and bladder or to speak or even to swallow. Also, she was rapidly losing her eyesight. Unfortunately, the one thing Ruth would not lose was her mind; she would remain mentally alert as she slowly and relentlessly became a prisoner within her own body.

I visited Ruth on a regular basis during the 2 or 3 years that she remained in a nursing home here in Rhode Island. As her physical health deteriorated, Ruth began to ask me to find some doctor who would put an end to her misery. During my last few visits before she lost the ability to speak, Ruth would scarcely talk about anything else: "Please, please help me. I don't want to live. I take no pleasure in anything anymore. Just find someone who will help me die." Ruth's daughter was with her when she spoke intelligible words for the last time. For more than an hour Ruth screamed: "Die! Die! Die! Die! Die! . . ." After that the only sounds she could make were those of a wounded animal. Ruth was unlucky. Though she could not speak or see or swallow or control her bowels or her bladder or move her arms or her legs or her hands or her feet, her heart was strong; she remained entombed within her rigid body for several months. As far as we can tell, Ruth was fully aware of her predicament almost until she died.

One could make a strong case that it would have been a moral and merciful act for a physician deliberately to kill Ruth. I use the words "deliberately to kill" so as not to disguise the fact that euthanasia is by definition an act of deliberate killing. Ruth had, in fact, made "a fully voluntary and persistent request for euthanasia." For a physician deliberately to kill Ruth in as painless a way as possible would seem to affirm the two central values that Dan Brock considers to be at the core of the central ethical argument for voluntary active euthanasia: 1) such a mercy killing would respect Ruth's "self-determination or au-

tonomy," for she had made it clear to her loved ones and to me that she wanted to die; and 2) killing Ruth before she became totally trapped within her own body would have preserved her "individual well-being" in the sense that through an act of euthanasia she would have avoided the indignity and agony of her final months.

Jewish tradition does not permit voluntary active euthanasia even in a case as extreme as Ruth's. In the authoritative code of Jewish law known as the *Shulchan Aruch* (*Yoreh Deah* 339.1, Gloss, Denburg translation) we find:

It is likewise forbidden to hasten the death of a dying man—eg, if one has been moribund for a long time and continues to linger on, we may not remove the pillow or the mattress from under him or do anything overt to hasten his death. However, if there is anything external that prevents his release from his death pangs, such as a clattering noise (of a woodcutter) near the patient's house, or if there is salt on his tongue, and these hinder the departure of the soul, it is permitted to remove them, for this is no direct act but only the removal of a hindrance.

I interpret this passage to mean that "passive" euthanasia is permitted while "active" euthanasia is forbidden. To turn to the case of the woman with amyotrophic lateral sclerosis (ALS) in Brock's article, removing the patient from the respirator is the removal of a hindrance to dying and is therefore permissible according to Jewish law. Why is this morally different from injecting the patient with a lethal dose of morphine, which Jewish law would forbid? The respirator is a hindrance to the process of *dying*, while the lethal injection is a hindrance to the process of *living*. From where I stand as a religious, though not traditionally observant Jew, this is no mere semantic quibble. Jewish tradition is trying to establish a boundary between those deeds that fall within the realm of morally responsible human behavior and those processes that ought to be left to God alone. While I make no claim of knowing with certitude what God says or wants, what I do hear, however faintly, in my encounters with the Holy Other is "I'm God, and you're not!" The physician is a partner with God when she removes a hindrance to the process of dying, or when she performs the manifold other tasks related to healing and the alleviation of pain. On the

While I make no claim of knowing with certitude what God says or wants, what I do hear, however faintly, in my encounters with the Holy Other is, "I'm God, and you're not!"

other hand, the physician is a *surrogate* for God when he gives the lethal injection. As a religious man, I view voluntary active euthanasia as a breach in the boundary that ought to separate human activity from the "activity" of God.

Although I try to live my life in relationship with God, I agree with Dan Brock for taking the "secular focus to be appropriate for public policy." Though I am opposed to legalizing voluntary active euthanasia for religious reasons, I think that a strong secular argument can also be made against legalizing voluntary active euthanasia. As Brock himself points out when discussing the removal of ALS patient's respirator, the moral rightness or wrongness of the deed is highly contextual. He sums up his analysis of the case: "one can either kill or allow to die with or without consent, with a good or bad motive, in or not in a social role which legally authorizes one to do so."

I would maintain that this sentence is in itself a powerful argument against legalizing voluntary active euthanasia. Every case of potential euthanasia is uniquely problematic; no law could possibly cover the range of circumstances in which euthanasia may or may not be appropriate. It is neither wise nor necessary for the state to give its imprimatur to legalized mercy killing, no matter how justified euthanasia might appear to be in a particular case. I would therefore suggest the more modest step of "decriminalizing" euthanasia. Such an approach leaves the burden of proof upon the physician and the family to justify, if need be, a deliberate though merciful killing. At the same time, decriminalizing euthanasia would help create a society that is more tolerant of those who argue that at times a merciful death is preferable to a prolonged though tortured life. For those of us who happen to be religious, we will continue to confront that awful and awesome mystery of how it could be that Ruth's scream is somehow an echo of the voice of God.

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Comments on "Euthanasia"

James T. McIlwain, MD

Professor Brock's essay makes a number of important points about the ethical problems surrounding euthanasia and assisted suicide. Rather than comment in detail on his arguments, with which I am in essential agreement, I thought it might be useful to reflect briefly on certain aspects of American society that make these matters so troublesome. Ethical dilemmas arise when deeply held values are in conflict and, because of the intense emotional climate surrounding such debates, opposing sides tend to elevate selected values to a status more absolute than they ever enjoy in daily life. The debate on euthanasia and assisted suicide is no exception and reveals a number of points on which our actions are not entirely consistent with what we say we believe.

Imagine how this debate might look to intelligent visitors from another planet. For example, they might be puzzled by the opinion that killing is always wrong because life is sacred and every individual precious. While this view is advanced by some as obligating us to sustain an individual's life at all cost, our society continues to send young people to die in dubious battle, tolerates absurd fatality rates on our roads and rewards the television and movie industries for entertaining us with the bloodiest mayhem imaginable. Some deaths would seem to be quite acceptable, as long as they are in a just cause, or a price of modern industrial life, or when they occur far away and to someone we don't know, or as fiction on a television or movie screen. Thus, when the alleged sanctity of life is used to argue that euthanasia and assisted suicide are absolutely excluded, we should be aware that it is being applied in a highly selective and essentially rhetorical way. It is unlikely that our extraterrestrial visitors would conclude from their own observations that we really hold life to be absolutely sacred.

Yet, curiously, when it comes to the fate of a particular individual, life becomes infused with something approaching absolute value, death becomes unacceptable and all must be done to stave it off. This, despite widespread lip service to the importance of the "quality of life" and assurances of assorted faiths that a life highly to be prized awaits us beyond this vale of tears. For life

as for money, more seems to be better. We Americans are sometimes accused of believing we should live forever and numbers of us do invest much time and energy into activities that we hope will avert the inevitable. Thus, death is failure or defeat, an event that must be postponed for as long as possible and certainly never hastened.

Reflecting on this, our visitors might reasonably surmise that another source of difficulty when it comes to euthanasia and assisted suicide is the pre-eminence of the private person in the value-fabric of our society, "individual self-determination or autonomy and individual well-being" as Professor Brock puts it. Our belief in the uniqueness and dignity of the individual is so deeply rooted that we grow uncomfortable when we hear of attempts in our own and other cultures to suppress individual impulses in the interest of family, tribe or society. Yet many are prepared to proscribe that primal, if poignant, expression of individual liberty, namely the freedom to decide when one's own life should end. Our visitors might well ask, "Who is served by such a proscription, the individual requesting release or those who would deny it?"

The answer is not simple, and several key aspects of the problem are discussed in Dr Brock's essay. When a society authorizes the deliberate termination of life for whatever reason, it accepts both the responsibility for the legitimate exercise of this function and the risk that such acts may be abused. Here, in the case of assisted suicide and euthanasia, the interests of the individual are not identical to those of society and the fear of misuse may seem to outweigh the expressed needs of a particular person. Society may say, "Sorry, but the implications of offering you release are so momentous for the multitude of living individuals that our concern for their welfare must take precedence over our desire to help you."

It is here that the "slippery slope" problem arises and the understandable concern that assisted suicide and voluntary euthanasia will slide irresistibly into socially imposed eugenics, with its attendant dangers to individuals who are seen as "marginalized" in our society. Here, though, if the larger society were to proscribe these practices absolutely, it would deny to these same individuals the release they might desire and seek. Even more problematic would be a selective proscription, designed to protect groups of otherwise competent individuals

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felt to be at risk, for here the shield for the group would be a barrier for the individual.

A related problem discussed by Dr Brock concerns the proper role of the medical profession in euthanasia and assisted suicide. Here, too, the discussion often circles the central difficulty, which is disagreement about, or even frank contradictions among, the core values that guide and inform medical practice. On a recently televised discussion of euthanasia and assisted suicide, a medical doctor argued that physicians should not "dirty their hands" with this business, because the public would lose trust in the profession. The assumption here seems to be that physicians can only serve the many if they deny certain kinds of help to the few. This rather lame argument ignores all the other behaviors of the profession that undermine public confidence, but it does illustrate the tension among values that compete for the physician's allegiance. The oath taken by graduates of the Brown University School of Medicine states, "The health and dignity of my patient will ever be my first concern." Having heard this, our visitors from another planet might find it difficult to understand how concern for public opinion could compel one to deny release to a competent patient whose health is gone and whose dignity is imperiled.

In my view, much of the trouble surrounding this debate arises from the missionary impulse that lies deep in the American psyche, spawned by popular religion and firmly rooted in the secular sphere. Moral values viewed as absolute must be imposed universally (lest perhaps doubts arise in the mind of the believers). This compulsion, so clearly present in fundamentalisms of various stripe, denies the autonomy of the individual. It also stands in the way of the accommodation described by Professor Brock, in which the decision "for death" is ultimately the prerogative of the patient, whose autonomy is safeguarded by institutional vigilance and whose needs are met by a caring physician.

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A Comment on Dan Brock's Essay, "Euthanasia"

Rev. J. Daniel Burke

"In the Decalogue God says 'Thou shalt not kill' or, in Hebrew, 'Kill not.' Period, as we say now: there is nothing about judicial execution, war, or self-defense. True, these are taken care of elsewhere in the Mosaic code, because the commandment is addressed to human beings, that is, to psychotic apes who want to kill so much that they could not even understand an unconditional prohibition against killing, much less obey it. Hence in its human and legal context 'Don't kill' cannot 'really' mean 'Don't kill': it means only 'Private murder is wrong because it is unpredictable and upsets established social authority.' The point is that it is in the unqualified order that we hear the voice of authority most clearly."

Northrop Frye

Elsewhere in the book, *The Great Code: The Bible and Literature*, from which the above quote was taken, Frye opines that even though it is in the unvarnished commandment we hear the voice of authority most clearly, "It is less important as a law than as a vision of an ideal world in which people do not, perhaps even cannot, kill." Where that leaves us I am not entirely sure, but it is certainly true human beings ascribe authority to the words, "Don't kill," whether that authority is God or some other source. And it is, alas, just as certainly true we, for the most part, proceed immediately to the enunciation of all those occasions when killing isn't really killing. Mind you, we do this also with those other most authoritative words we hear, the ones concerning the telling of the truth, the keeping of promises, and respect for the other, the other's person and, by extension, property. It is an ambiguous world out there for all except the comparatively few dyed-in-the-wool absolutists or, perhaps, the truly pure in heart, the saints. The rest of us yield sooner or later to the uncertainty and indeed we of the 20th century have made a kind of governing principle of it oxymoronic as that may seem. But the commandments, and particularly the sixth, the one that prohibits killing, or murder as it is more ambiguously translated, continue to haunt us. Consequently, when any fresh circumstance for the taking of life arises, it is appropriate to feel the

need to proceed very cautiously if at all.

Euthanasia, though not a new issue in human affairs, nevertheless has sprung up in our era as a kind of a fresh circumstance in the taking of human life. This, of course and ironically, is due to the unintended side effects of the success of modern medical science. Things like defibrillators and ventilators, the wonders of modern surgery, radiology, and pharmacology not to mention the oncoming miracles of genetic therapy all play their brilliant parts in the preservation of human life. And every one of them also has its share in the creation of situations in which either instantaneously or over time weal can convert to woe. And extravagantly burdensome woe it can be. Increasingly we find we have preserved lives whose chief characteristics turn out to be exquisite pain or the vegetative state. Disease and disorder have ever been the authors of such suffering, but with that we must now factor the augmentation of our

It is an ambiguous world out there for all except the comparatively few dyed-in-the-wool absolutists or, perhaps, the truly pure in heart, the saints.

own iatrogenic contributions and add the burden of increasing foreknowledge. We are learning and will only learn more about whether we are headed for all manner of affliction or incapacity beginning with AIDS and now, apparently, Alzheimer's disease and continuing through the growing alphabet of time-delayed scourges, which are literally or figuratively life-ending. The contemplation of such a menu of travail brings with it increasing reflection on the question of how much of this is reasonable to require humans to endure. All this and we haven't even mentioned the economics of the matter. Our moral sensibilities incline us to rule this way down the scale, if not out as a factor, but it will not stay put away. You may get it off the screen, but not out of the system. Finally, however, there comes the question of what to do concerning those situations when mortally afflicted or threatened human beings (as, for instance, in the case of encroaching Alzheimer's disease) declare their strings of endurance exhausted and yet require assistance in the planned

When it comes to morals and metaphysics, I have found it to be the case that any truth pressed to its limit will become a half-truth, including this one.

ending of their lives: the case of voluntary euthanasia, the issue addressed in Dan Brock's essay.

Since he confines his remarks to this issue, I shall try to do likewise. I, however, shall not restrict myself to the secular realm but rather move through and beyond it in an attempt to establish a reasonable, religious basis for my own conclusions about the morality of euthanasia.

It should be said at once my conclusions are roughly in agreement with those of Professor Brock. That is, subject to necessary safeguards and constraints analogous to those developed in connection with the establishment of advance directives concerning life-sustaining care, I believe that voluntary euthanasia can and should be considered a morally responsible act. This would be true, as Professor Brock indicates, whether the agent is the self or another. And, as indicated above, I would expand the category of cases to include not only the dying patient, but the as-good-as dead or dying patient, the one facing imminent or projecting to sometime certain or actual descent into a permanent vegetative state. I emphasize this acceptance would be true only in cases involving a voluntary pre-selected act made in a clear, consistent and unequivocal manner by the choosing subject, and meeting the standards for such action deemed acceptable to the community.

I would further note I do not come to this position because I am comfortable with it. In fact, seeing it in print registers disturbingly high on my uneasiness scale. But there are, I have found, some things we probably never will or should be comfortable with in this ambiguous pile of experience we call life. I come to it for reasons I hope to make clear including the fact I am even less comfortable with the options: prohibition or institutionalized looking the other way.

In the effort to find solutions to ethical dilemmas, moralists continue to pit rules against rules, consequences against consequences, and rules and consequences against each other in an ongoing struggle for su-

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ABBREVIATIONS USED:
AIDS: *Acquired immune deficiency syndrome*

premacY in persuasiveness. That is entirely as it should be. One hopes the issue of all this will be a consensus forged by the best of human reflective abilities hammering away at a given problem. And so it generally is. Unless, that is, it is disrupted and derailed by the entry of the character I refer to as the "spiritual imperialist." In secular terms this is the one who brings a or, more accurately, the categorical imperative or its descendant to the effort. In religious terms it is the one who has been given possession of the appropriate divine command in the matter. In either case it is effectively the end of the dialogue as Alasdair MacIntyre and others have noticed, although I am not sure they have all that accurately identified the toxic agent here or fully appreciated its ubiquity. When it comes to morals and metaphysics, I have found it to be the case that any truth pressed to its limit will become a half truth, including this one. In treating the most difficult questions we apparently must put the half-truths together in order to arrive at a whole.

More and more we find we have preserved lives the chief characteristics of which turn out to be exquisite pain and/or the vegetative state.

What that means, if I have understood these things correctly, is that there are no such things as undiluted categorical imperatives or divine commands in the sense that they can be demonstrated to be conclusive in all matters pertaining to a question at issue. They are chimeras born, no doubt, of the deep human longing to be able to settle troublesome problems definitively. This need blinds us to the facts that:

1. An imperative has ultimately to be defended by resort to its opposite member, a consideration of the consequences of doing or not doing what it prescribes (or, more devastatingly, it can be defended by resort to the use of force, in which case the whole moral enterprise tends to go into the tank); and
2. When it is defended by resort to its opposite member, it loses its essential character as categorical directive. An example of this in the matter at hand is the defense of the prohibition against voluntary euthanasia by use of the "slippery slope" argument, a list of rightly to be feared consequences of voiding the ban on euthanasia. We may agree or disagree about what the rule on euthanasia should be

according to the consequences, but let's not settle the matter by imagining we can subsume the argument at a stroke.

. . . there are no such things as undiluted categorical imperatives or divine commands in the sense that they can be demonstrated to be conclusive in all matters pertaining to a question at issue.

Let us return then to the issue of voluntary euthanasia and why I believe it can, in certain circumstances, be affirmed as a morally acceptable act. Morals or, more pointedly, ethics are patterns of belief and behavior concerning what is good and bad, right and wrong, virtuous or reprehensible. They arise within or are imported into an ethos as the word implies. Community and relationship are presumed and the maintenance of the highest quality of relationship in community is surely one of the principal aims of the ethical enterprise. Abandonment, on this view, is likely to be one of the least valued behaviors any member of the community could exhibit. It seems to me to be a weak to vanishing emblem of the reality, let alone the value, of relationship to abandon someone who is *in extremis*. And this, it further seems to me, constitutes the effect of refusing to allow the possibility of euthanasia. I repeat, this possibility, or freedom to act without stigma, should not be accorded to anyone who asks. It applies to those whose subjective appraisals of their unbearable circumstances, affirmed by carefully drawn objective criteria of a compassionate community are defined to be in a situation extreme enough to warrant it.

It might be argued abandoning someone to death is more blameworthy than abandoning them to further suffering, even in the most extreme circumstances. A poignant quotation from Ronald Dworkin I recently read tends strongly to reinforce this hesitation. "Death", he said, "has dominion because it is not only the start of nothing, but the end of everything . . ." It gives one almost infinite pause until one realizes it is after all a faith statement on the order of, say, "For I know that my redeemer lives, and that he shall stand at the latter day upon the earth; and though this body be destroyed, yet shall I see God; whom I shall see for myself and mine eyes shall behold, and not as a stranger." (Job 19:25-27a), or, "Here and now, dear friends, we are God's children; what we shall be has not yet been disclosed, but we know that when it is

disclosed we shall be like him, because we shall see him as he is." (1 John 3:2). To give assent in the former case we are called to rely on our senses and nothing more. In the latter case it is our intimations and intuitions and nothing more. The point is we cannot be sure of what it is we are consigning ourselves to either way. That old uncertainty again! One can almost believe, and I indeed do assume, it is God who built it into creation. It is *sine qua non* of living life as a trust or faith exercise to which the biblical narrative from beginning to end enjoins us.

No more, in the case of voluntary euthanasia, can we be sure which form of abandonment is the worse one until we decide for ourselves. Speaking from within the Christian dispensation, I find this conclusion and this responsibility to line up quite coherently with the cryptic instruction (or is it an injunction?) given by Jesus to his disciples as mentioned three times in the gospels: Matthew 16:18-19 and 18:18; and John 20:23. Whatever we bind or loose, retain or forgive on earth, will be regarded thus in heaven. I interpret this as an instruction to be worked out in the community and not the preserve of any hierarchy alone.

It might be argued that abandoning someone to death is more blameworthy than abandoning them to further suffering, even in the most extreme circumstances.

Like most, perhaps virtually all, of us I already own a patchwork of stands on the taking of human life (certainly sympathetic to self-defense, grudging defender of the use of—some forms but not all—armed force in war, and opposed to capital punishment). The question before us is whether it is time now to add to that patchwork. The answer we give to that, I think, really and finally relates to what we believe about life and about death which in turn is the outcome of the dance between what we fear and what we hope.

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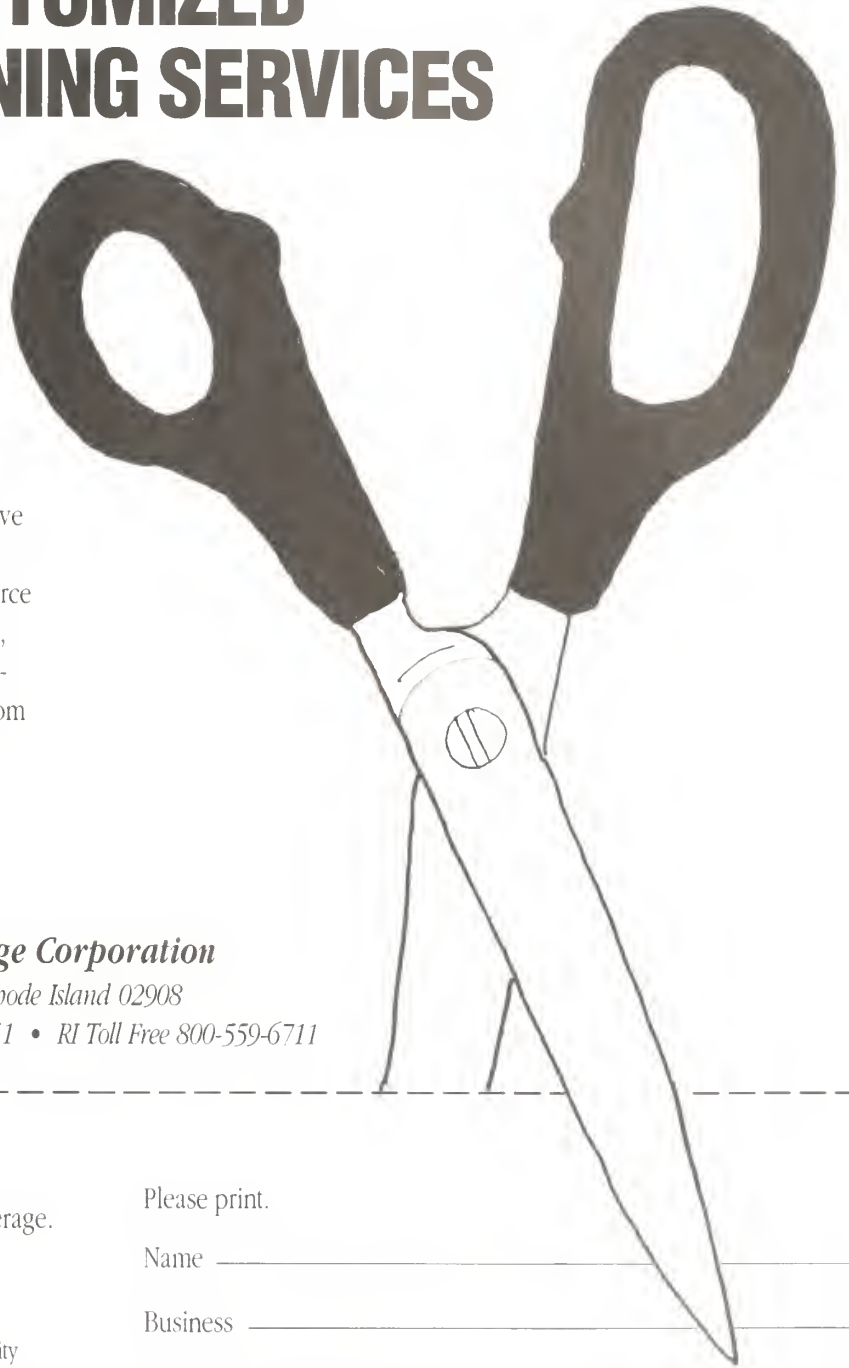
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HEALTH BY NUMBERS



Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Medical Waste Inspections in Rhode Island

During the summers of 1987 and 1988, needles, syringes, tubings, blood vials and other waste associated with medical care appeared on many beaches of the Northeast coast. As a result, Congress passed the Medical Waste Tracking Act in 1988, authorizing the US Environmental Protection Agency to enact a pilot program and regulate the management and disposal of medical waste. Rhode Island joined four other states as participants in this program, which expired in June 1991. Subsequently, the RI Department of Environmental Management (DEM) issued its own regulations, the "Rules and Regulations Governing the Management and Handling of Medical Waste in Rhode Island."

Rhode Island's regulations identify several categories of regulated medical waste (RMW), such as cultures and stocks of infectious agents, pathological wastes, human blood and blood products, used and unused sharps (needles and syringes), certain animal waste, and isolation wastes (from extremely contagious diseases). The regulations govern many facets of RMW management, including packaging, labeling, storage, and disposal, and impact health care providers identified as medical waste "generators" (Table 1).

The RI Department of Health (DOH) is responsible under contract to DEM for medical waste generator inspections to ensure compliance with the regulations. Inspections are performed unannounced and include all types of generators within the state. The first inspection is generally used as an educational visit, unless there is an imminent public health risk (improper needle or syringe disposal). However, because this is a regulatory program, all violations must be corrected by the generator.

The results of the first 150 medical waste inspections completed by the DOH under DEM's regulations are presented in the two accompanying figures. Figure 1 demonstrates the total number of facilities inspected and identifies those facilities without any

Table 1.—Medical Waste Generators and Amount of Waste Generated, Rhode Island, 1993.

Facility type	Number	Avg. pounds RMW generated/month
Hospitals	17	7275*
Clinical Laboratories (includes drawing stations)	51	100
Ambulatory Care Facilities	42	300
Physicians	3132	35**
Dental Offices	436	10
Long-term Care Facilities	106	65
Funeral Homes	106	15
Veterinarians	104	40

* varies from 650 to 10,000 pounds per month

** varies from 5 to 75 pounds per month, depending on the specialty

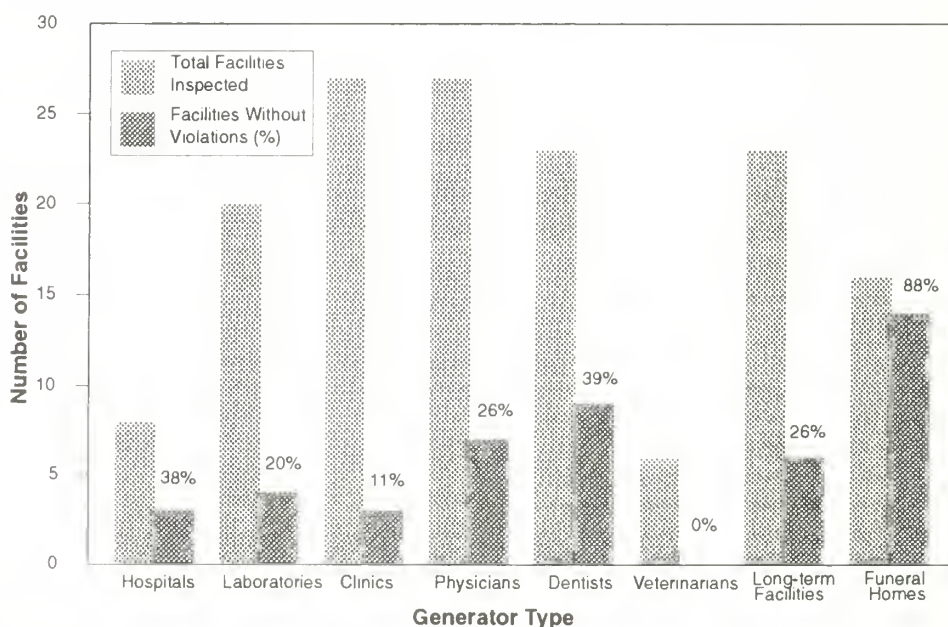


Fig 1.—Medical Waste Generator Inspections, Total and Percent without Violations, by Type of Generator, Rhode Island, April 1992-October 1993.

violations of the regulations. For all types of facilities inspected, 31% were found to have no violations. Funeral homes had the highest compliance rate for any category of generator, with 88% having no violations.

Figure 2 compares the distribution of the three most common types of violations found during inspections with generator type.

(Note the percentages of violations by facility type may not equal 100%, either because of other types of violations not identified here or because of multiple types of violations per facility). According to the regulations:

- Facilities producing or shipping more than 50 pounds of RMW per month must

use tracking forms to establish a "paper trail" of the facility's medical waste. Violations may include missing copies of forms or incomplete information on the forms. All facilities except hospitals had some tracking form violations.

- RMW must be identified (labeled and marked) with either the biohazard symbol or the words "medical waste," and with the generator's identification. Of all inspected facilities, 44% had some violation in this category.
- RMW storage areas must be inaccessible to the general public and clearly marked as containing RMW. Of all generators inspected, 22% showed violations in this area.

In addition to facility inspections, the medical waste programs within the DOH and the DEM provide guidance to the general public, whose medical waste is not regulated. This has included publishing and distributing a pamphlet entitled "Home Guide for Disposal of Medical Wastes" and establishing a home-generated sharps return program with pharmacies in three Rhode Island communities.

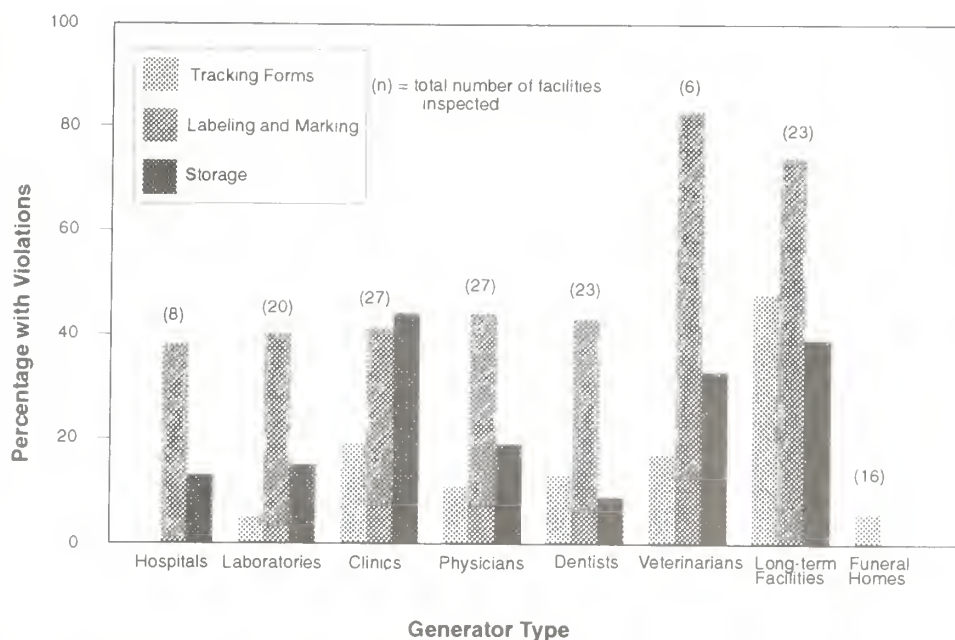


Fig 2.—Percent of Medical Waste Generator Inspections with Selected Violations, by Type of Generator, Rhode Island, April 1992-October 1993.

There must be a good reason why



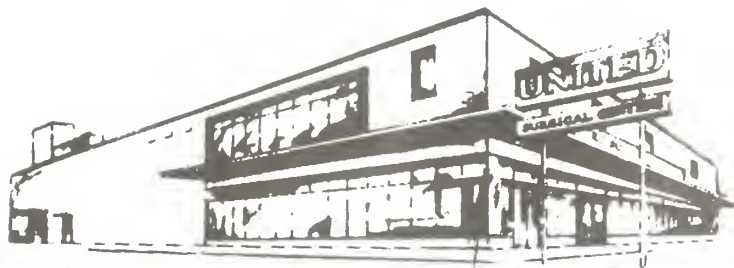
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CLINICAL POINT OF VIEW

Medication Noncompliance: A Significant Problem and Possible Strategies

Henry M. Litchman, MD

Medical literature defines a patient's compliance as the "voluntary cooperation of the patient in following a prescribed regimen." Studies indicate that between 30% and 50% of patients are non-compliant in whatever condition is studied.^{2,3,14,20} The definition is probably too narrow and should be understood in behavioral terms, whether it involves medication, following diets, or changing prescribed lifestyles as recommended by the treating physician.²¹ Since this is a behavioral problem, the physician has to consider that there are varieties of noncompliance, ranging from complete, partial, erratic, to overusage.²⁵ Noncompliance also may be unintentional. In all of its varieties, this problem is significant in maintaining a patient's health.

In spite of improved patient education, physicians must realize that many factors contribute to noncompliance.

The effects can be found in any age group. Younger patients reportedly take more self-medication.²⁴ With increasing age, medications become more important to increase function and quality of life.³ Patients over 65 years old may consume 12 to 15 medications a day, including over-the-counter drugs.²³ The complexity of medication prescribing is directly related to noncompliance.¹⁸ It is expected that in the future, the problem of noncompliance, adverse reactions and drug interactions will increase.^{22,6}

Elderly patients must deal with multiple medications at a time when they are experiencing a declining ability to remember and program their dosage schedules. Other physical limitations such as poor vision and hearing may also play a role in increasing noncompliance.^{21,4}

Most physicians believe that they understand their patient's behavior regarding medication usage. Practical experience and review of the literature suggest otherwise. It has been estimated that 20% of prescrip-

tions are never filled.² In one study of patients over 60, almost half admitted non-compliance.³

Although the elderly population is about 12%, they experience 30% of the adverse drug reactions with an increased incidence in cognitively impaired patients on psychoactive medications.²³

Physicians should be aware that some patients in nursing homes may be on medications without their direct participation in drug decisions.^{12,23}

In a survey of the elderly of their hospitalizations, 28% were drug-related. Medication noncompliance accounted for 11%, and 17% were from adverse drug reactions.⁴

Awareness is one of the keys to prevention. In a population of patients on pre-

... the problem of noncompliance, adverse reactions and drug interactions will increase.

scribed nervous system drugs, 81% reported taking their medication three out of four times.¹³ Emergency room admissions revealed that 10% to 20% were related to over-medication. Some patients were thought to be suffering from Alzheimer's disease until the over-medication diagnosis was established.¹²

In a retrospective study of asthmatics, only 60% were found to be in the therapeutic range of treatment.¹⁴

Infection presents another problem. Compliance with antibiotic regimen is poor. This is relevant in that more patients are discharged prematurely while still on medications.^{5,10}

Statistics compiled by the US Department of Health and Human Services indicate the same trend toward medication noncompliance.

The magnitude of the problem becomes evident when we consider that the aged get more than two and one half times more prescriptions than younger adults, amounting to as many as 13 prescriptions per year. Among nursing home residents, 30% are on

In a survey of the elderly, 28% of their hospitalizations were drug-related.

as many as 8 to 12 drugs per patient.²³

Medication and Trauma

The other aspect of the problem yet to be satisfactorily quantified is the surgical sequelae of medication. Barbiturates are frequently implicated in patients who fall when getting out of bed at night. Under their influence, patients can be confused.

More common now is the use of benzodiazepines and their derivatives, which also tend to be addicting. Their use is increasingly frequent in medical practice. It has long been estimated that 1% to 3% of the population are using them on a long-term basis. One significant side effect of these drugs is memory loss, but no data exists on whether it causes noncompliance. Careful monitoring is advisable.

Benzodiazepines can also predispose patients to fall.²³ Studies on Valium show that an elderly patient is twice as likely to fall.¹²

Identifying the Variables

When prescribing treatment, the physician must consider that the patient may not be able to follow instructions. This can occur in any age group but becomes more significant in the elderly. Common to all prescribing, the responsibility is for the physician to identify those variables that contribute to noncompliance.¹⁴ This includes how knowledgeable the patient is of the disease.^{4,6,8} In addition, many patients cannot afford to fill their prescriptions. Rather than risking noncompliance, less expensive or generic drugs could be prescribed.

The incidence of noncompliance may be cultural^{4,19} or ethnic.⁹ Noncompliance is reputed to be more frequent in members of large families.²⁴ Significantly higher rates are found among elders living alone.⁴

Strategies to Reduce Noncompliance

Prescribing

Changing the frequency and duration of prescriptions have been well documented

Rhode Island Medicine

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to improve compliance.^{7,9-11,14} In one study, the compliance went from 59% on a 3-a-day regimen to 83.6% on a once daily regimen.⁷ If the dose is required daily, it has been recommended to give it in the morning.¹⁹

Education

Written and oral instructions are both essential for some patients. One drug store chain has started to enclose written instructions with the prescription when filled. It includes dosage schedules prescribed by the physician and awareness of common side effects. It has been shown that one of the most effective prevention strategies is in educating the patient about the illness.^{21,13}

Team Approach

We often forget to use other participants in the care of the patient. Family members, pharmacists, and visiting nurses can play a significant role in completing the treatment team.^{1,3,9,11,18,23}

Motivation

A physician's advice concerning changes in lifestyle has been disappointingly ineffective.¹⁵ The physician should be a motivator and educator. Compliance is linked to satisfaction with medical care.³ It is the ability of the doctor to gain the trust of the patient, by exhibiting a genuine concern to patient's stressing the importance of compliance.^{2,15,19,21} The doctor who smokes is not a good role model for a patient who has a disease related to smoking. Doctors themselves are notoriously poor patients and "their level of compliance is lower than

The doctor who smokes is not a good role model for a patient who has a disease related to smoking.

other people with the same condition."²

The most important factor in motivation is a shift in power and control from the doctor to the patient.¹⁵

Identification

Identifying the patient who is non-compliant is not always easy.⁸ In a study of hospitalized patients, 32.7% had a history of noncompliance usually due to forgetfulness.⁴

Eventually patients who are not responding to treatment or develop complications will become evident. For prevention, physicians should record requests for prescription refills, which may signal that the unit numbers are not in keeping with the number expected.²⁰ Since patients tend to use mul-

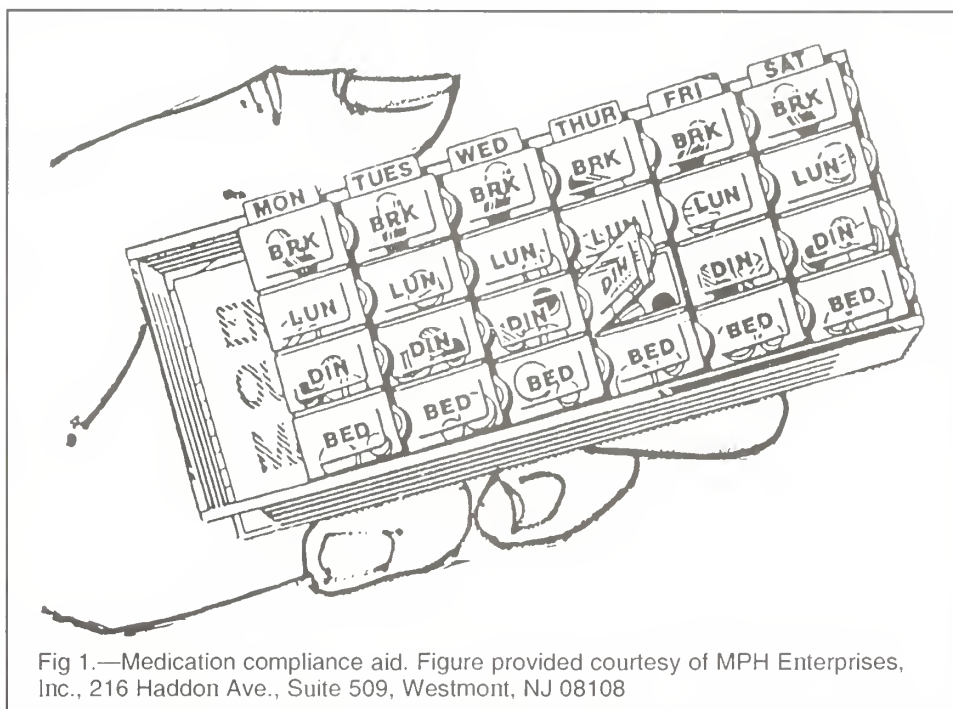


Fig 1.—Medication compliance aid. Figure provided courtesy of MPH Enterprises, Inc., 216 Haddon Ave., Suite 509, Westmont, NJ 08108

multiple pharmacies as well as multiple physicians, the history should include the names of other caregivers and a listing of current medications. There is a slightly higher incidence of adverse drug reactions in patients using multiple pharmacies.⁴ Over-the-counter medications should be included since they can be potentially harmful if used incorrectly.¹² This will require updating.

It is difficult to judge a patient's medication compliance in the clinical setting. Pill counts and metabolic markers are usually not reliable indicators of compliance.¹⁶ On average, most patient's compliance lapses appear to be random.¹⁷

Compliance Aids

Despite its difficulty, assessing medication compliance is still an important factor in maintaining a patient's good state of health. Another strategy, less frequently discussed, is the use of compliance aids such as medication calendars, special caps and packaging systems to help patients keep track of their doses.^{1,7} Most, however, are not practicable or economically feasible.

The patient has to be provided with a simple method to monitor the medication regimen. The aid should be simple, well marked, and easy to operate. If there is a memory deficit, the patient can always look at the aid to see if the dose was taken. This may require the assistance of other health care professionals or family to ensure success.³ The device can be loaded by a family member or a home health care worker who would monitor the compliance.

Currently, Medicare considers compliance aids a "convenience" item "not rea-

sonable and necessary for treatment." (*Medicare Carrier Manual*, Section 2318. Considering the economic consequences of non-compliance, this may be shortsighted. Non-compliance has been identified as "one of the most serious and costly epidemics in America today."²

There are several medication containers on the market with different features. These containers should be sturdy and contain a

Many older patients require some mechanical aid to assist them in taking the required doses at the right time.

card listing the contents, clearly labeled for the visually impaired. The container should have a lid for each dose compartment that can be closed with a clear "click" to prevent spillage. The latch should be easy to operate by the tremulous or arthritic fingers. Another feature to be looked for is the ability to remove a day's dosage when going out of the house for the period when doses are required.²⁶ (See Figure 1.)

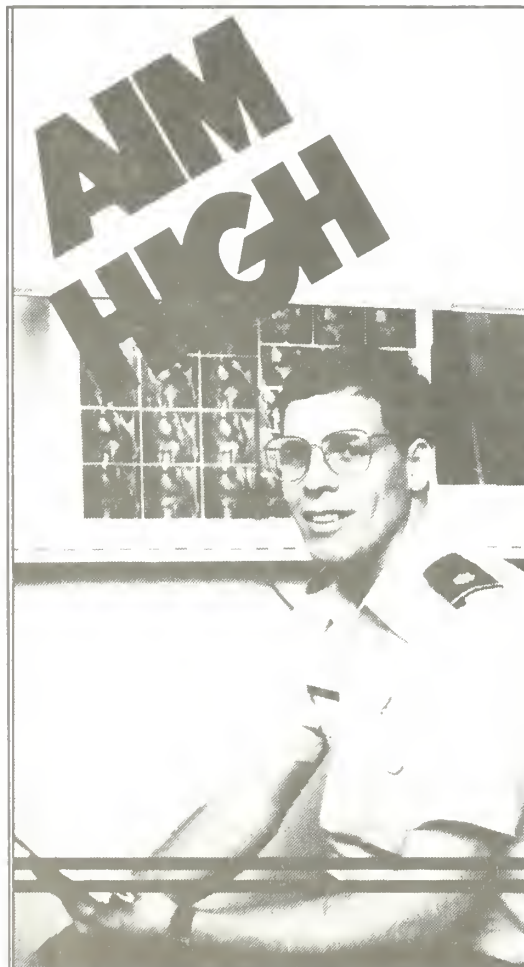
Summary

Medication noncompliance is a significant public health problem with both economic and quality of life dimensions. The physician should be aware of the frequency of the occurrence and develop strategies to reduce its incidence. This includes simplification of prescription practice, patient education and adequate instructions. The physician has to accept the role of a motivator as a part of the education process.

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

90 Years Ago (December 1903)

An article on the use of an exclusive milk diet in the treatment of certain diseases is offered by Max B. Gomberg, MD. The author observes that the use of milk in the therapies for phthisis, gout and other chronic affections was described repeatedly by such ancient authorities as Galen, Celsus and Hippocrates. The author also notes, from Elizabethan sources, the therapeutic merit of human breast milk in neutralizing "consuming fevers" and restoring potency to elderly males. After a discussion of the role of proteids, carbohydrates and hydrocarbons in human digestion and metabolism, the author then proposes that such diseases as diabetes, gout, rheumatism and obesity are best considered as direct consequences of deranged nutrition. He notes that, "... an excessive amount of sugar in the blood is enough to justify us in the opinion that the disease is primarily caused by perverted metabolism whatever other complications may be associated with it." Furthermore, he observes, "In rheumatism and lithaemia we observe the consequences of perverted nitrogenous metabolism. In obesity the vitality of the cell itself is so affected by deranged nutrition that it cannot efficiently complete its metabolic function and produces a fatty substance that can neither be used nor discharged." With regard to the special features of milk, the author states: "Milk is, it must be understood, itself a finished product of metabolism. The elements of nutrition which it contains are not specialized for contractile, automatic, or secretive purposes. It is almost ready to be used when it reaches the vital cell since the work of metabolism is already begun before it is even digested. It leaves, therefore, very little for the weakened or perverted cell to

do. Taken as a whole the parts of which it is composed are ideally proportioned, allowing nothing to chance, habit, environment or perverted function. It follows, too, that its debris do not add to the burden of the system in their elimination." Milk is thus "a regulator of nutrition and as such occupies a rather unique position in a long list for therapeutic agents." The author then cites a few clinical cases where a milk regime was of clear therapeutic value. He concludes: "I do not recommend the exclusive milk diet as a panacea for all ills. But I do think from the experience that I have had of it and from the experience of those whom I have cited that milk is a useful addition to our list of therapeutic agents and that it deserves to be considered seriously in the diseases dependent upon or aggravated by an abnormal condition of metabolism or nutrition."

G. Edward Buxton, MD, writes on rupture of the uterus, noting first that it is the most appalling accident of midwifery, particularly since it can neither be "foreseen nor averted." The article then provides the reader with a few examples of uterine rupture, occurring during labor pains resulting in the extrusion of interstinal loops through the uterine rupture. In the four cases summarized, the externalized loops were mistaken for umbilical cord and unfortunately severed by the obstetrician, resulting in the death of the patient in each of the four cases.

The minutes of the Rhode Island Medical Society are included in this issue of the *Journal*. Concerns were expressed regarding the patenting of medicinal chemicals thus enabling foreign manufacturers to discriminate unfairly against domestic drug

companies. Dr Herbert Terry exhibited to the Society membership various kinds of stones surgically extracted from the human bladder including those of cysteine, phosphate, or uric acid composition. Dr J. McCormack of Kentucky addressed the Society on behalf of the American Medical Association. He noted that less than 25% of the 120,000 practitioners in the United States were members of any medical society and that a stricter control of itinerant and quack physicians was imperative. He outlined the value of a central association representing the entire profession, an association that might be instrumental in establishing higher standards for the practice of medicine and the licensure of practitioners. Resolutions demanding enactments of laws controlling the sale of blank pistols, and ammunition were outlined following the news that there were over 400 deaths from tetanus during the Fourth of July celebrations in 1903.

50 Years Ago (December 1943)

Alexander P. Aitken, MD, describes a new inpatient facility called a rehabilitation center. This unit was established by a large insurance company in Boston expressly to care for workers disabled following industrial accidents. All patients entering the facility did so voluntarily. The author describes the mission of the center and the clinical details of the first 63 admissions. Some of the more common diagnoses encountered were: subdeltoid bursitis, ruptured disc, fractures involving an extremity, amputations, compression fracture of the spine and other orthopedic injuries. The author concludes: "The idea of rehabilitation of the injured workman is relatively new. Much has yet to be learned in the proper handling of these cases, particularly from



the view of work therapy."

Following federal legislation allowing "payment of stipulated sums to hospitals and payment of stipulated sums directly to physicians for maternal care to mothers and pediatric care to children under 1 year of age to men in the armed services," the Rhode Island Medical Society created an ad hoc committee to assist in formulating a state plan to implement this Emergency Maternal and Infant Care [EMIC] Program. Eligibility was restricted to the dependents of the four lowest military ranks.

Anthony V. Migliaccio, MD, summarizes a local meeting that had discussed the medical and surgical treatment of varicose veins, with consideration, also, of pulmonary emboli, and gastric and duodenal ulcers.

The Committee on Problems Due to the Shortage of Physicians, chaired by Elihu Wing, MD, provides a summary report of its activities. The committee first notes that there already are 50,000 US physicians in the armed forces. Of the 626 civilian physicians still remaining in Rhode Island, 28 are no longer in practice and 223 are over 45 years of age. "Nationally there have been statements to the effect that the ratio of 1 doctor to every 1500 population is as safe one for the protection of civilian health. If such a yard stick were applied to Rhode Island today we would be more adequately protected, with an average on the present figures of 1 doctor to approximately every 1140 persons."

The Committee on Industrial Health, chaired by Charles L. Farrell, MD, reports on medical problems incurred by women working in industry and makes certain recommendations to lessen workplace trauma to this population.

News from the war fronts and placement information concerning Rhode Island physicians in uniform are printed.

25 Years Ago (December 1968)

The lead article by Austin Daley presents the serious nature and magnitude of the problem of solid waste disposal in Rhode Island. The author [in charge of the Health Department's Division of Air Pollution Control] concludes: "... this presentation can be reduced to two aspects: the effect on our health and the willingness of our people to provide the financial means for correcting this lamentable situation ... the people of this congested state should realize that efficient regional landfills and incinerators are sound answers for only a few decades. With the population explosion, urban sprawl and spiralling per capita daily waste generation, we will soon run out of space and time."

Mary D. Lckas, MD, describes the medical experiences with Project Hope in Ceylon. The USS Hope, with a fully equipped hospital of 150 beds and a medical, nursing and ancillary staff of about 135 personnel, had previously visited Indonesia, South Vietnam, Peru, Ecuador, Guinea, Nicaragua and Colombia. The author describes the nature of otolaryngologic procedures carried out about the ship and the many acts of goodwill accomplished by the volunteer staff.

An article on traumatic effects of the cranium repaired by autogenously derived split rib cranioplasty is authored by Howard S. Sturim, MD.

Luis Arce, MD discusses the diagnostic and prognostic value of lactic acid dehydrogenase (LDH). Albert Kalderon, MD, discusses macroscopic autopsy diagnosis of early myocardial infarction using a ditetrazolium chloride dye called Nitro-BT.

Henry M. Litchman, MD, describes the more recent workmen's compensation laws that have more clearly defined the rights of employees to financial benefits.

YOCON[®] YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubiaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

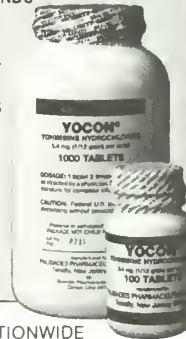
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol*. 1991; 14:146-151.

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and Lactation: Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis, hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin, the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability of therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and excessive prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with placebo.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2 year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of liver adenomas in mid- and high-dose males and females. Adenomas of the eye (Harderian gland [a gland of the eye of rodents]) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/– mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/m²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo

The following effects have been reported with drugs in this class

Skeletal: myopathy, rhabdomyolysis

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting

Reproductive: gynecomastia, loss of libido, erectile dysfunction

Eye: progression of cataracts (lens opacities), ophthalmoplegia

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS)

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

Skeletal Muscle and PRECAUTIONS: Drug Interactions.

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

THE PRAVACHOL® DIRECTION
IN LIPID MANAGEMENT

Effective lipid management doesn't have to be tough



- Improves key lipids — significant reduction in LDL-C¹
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food


PRAVACHOL®
pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate. Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



Bristol-Myers Squibb Company

